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Original Communications

STUDIES ON AIR-BORNE INFECTION IN A HOSPITAL WARD

I. THE EFFECT OF ULTRAVIOLET LIGHT ON CROSS-INFECTION IN AN INFANTS' WARD

HARRIET E. SOMMER, AND JOSEPH STOKES, JR., M.D.
PHILADELPHIA, PA.

POSSIBLE air-borne transmission of certain respiratory infections has been demonstrated by experimental means and through epidemiologic observations. Sterilization of contaminated air is, therefore, an urgent problem, particularly in places such as hospitals, where pathogenic bacteria are more concentrated and the resistance of the patients may be lowered. The fact that disease-producing organisms can be recovered readily from the air of hospital wards has been pointed out by numerous studies.[1-6]

Experimentally, ultraviolet irradiation has proved effective in destroying air-borne droplet nuclei containing pneumococci, hemolytic streptococci,[7, 8] tubercle bacilli,[9] influenza virus type A,[10, 11] and other organisms. Through the basic studies of Wells and Wells[12] and of Hart,[13] ultraviolet light has been applied with encouraging results to practical problems, such as irradiation of hospital wards, operating rooms, and schools. Within recent years, studies on ultraviolet irradiation and its effect on hospital infections have been carried out in several institutions, including The Children's Hospitals of Boston and Philadelphia, The Home for Sick Children, Toronto, and The Cradle, Evanston, Ill. On the whole, these and other studies have given encouraging results.[6, 14-17] However, there have been some inconsistent findings. For example, del Mundo and McKhann,[6] at The Children's Hospital of Boston, reported the effectiveness of ultraviolet light in preventing air-borne infection, but in the following year, at the same hospital, Brooks and co-workers[18] found little difference in the number of cross-infections between the irradiated and nonirradiated wards.

From The Department of Pediatrics, School of Medicine, University of Pennsylvania, and The Children's Hospital of Philadelphia.

The present study in The Children's Hospital of Philadelphia has been in progress since 1939. The object was to determine the effectiveness of ultraviolet irradiation on the number and kinds of air-borne organisms and on the frequency of infections contracted within the hospital. In the course of this study it became apparent that irradiation in the experimental ward had some beneficial effect on the air of the nonirradiated control ward because of an open corridor forty-seven feet long between the two wards. These data may explain some of the conflicting results reported in the literature, particularly those found at The Children's Hospital of Boston. In those studies, the reduction of air-borne bacteria during the season of respiratory infections in the control ward points to the exchange of air between irradiated and control wards, with a beneficial effect on the latter.

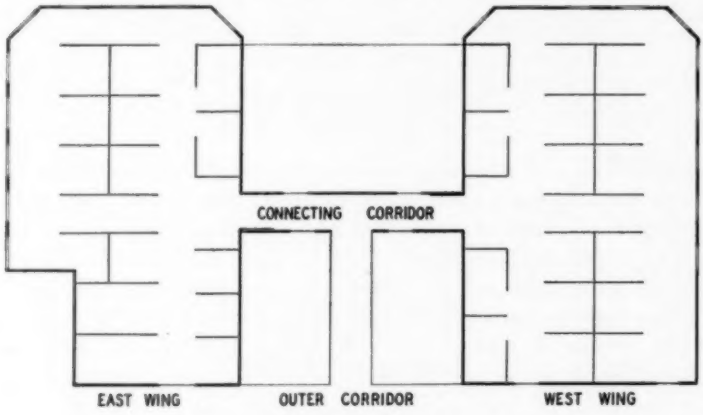

Fig. 1.—Floor plan of infants' ward.

METHODS AND MATERIALS

Two almost identical wings of the Infants' Ward of The Children's Hospital of Philadelphia, as seen on the floor plan (Fig. 1), were chosen for the experiment. These are divided into cubicles which are enclosed on three sides by partitions extending seven feet from the floor to within four feet of the ceiling. The design of the ultraviolet installations above the entrance to the cubicles of the west wing (Fig. 2) is similar to that found at The Cradle in Evanston, Ill., and later installed at The Children's Hospital of Boston.[19] Individual gown technique was applied by the nurses in all cubicles. Masks were not used for various reasons.

Nasopharyngeal swabs made from 34-gauge nichrome wire and throat swabs of 20-gauge copper wire were tipped with cotton. Since blood agar plates were inoculated immediately on the wards, dry swabs were used. The right and left sides of the nasopharynx were swabbed and

streaked together on a blood agar plate. Throat swabs were cultured on separate plates. Nasopharyngeal and throat cultures were prepared in duplicate. One of each was incubated aerobically, the other in an atmosphere of N_2 + 10% CO_2 for eighteen hours at 37° C. and then examined for the presence of pneumococci and beta hemolytic streptococci. Pneumococci were typed by the Neufeld-Quellung reaction either directly from the plate or from subcultures in glucose infusion broth. The beta hemolytic streptococci were grouped by Brown's technique.[20*]

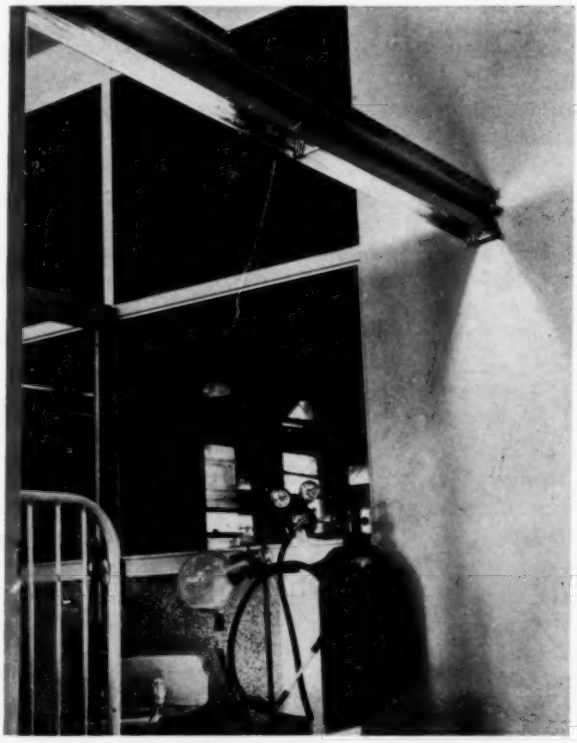

Fig. 2.—The ultraviolet light installations above the entrance to the cubicles of the west wing of the infants' ward.

The Wells air centrifuge was employed for both quantitative and qualitative studies of the air of the wards. The air-flow of the centrifuge was set at 1 cu. ft. per minute, and three successive five-minute samples were taken at each location. In all experiments in which the number of organisms in a given amount of air was determined, the standard technique for handling blood agar tubes was used (Part II†),

*We are indebted to Dr. Rebecca C. Lancefield for supplying the group-specific immune sera.

†Part II appears on p. 577 of this issue.

and the average count of three runs was considered representative of the number of attainable organisms at the location. For determining the kinds of organisms present in the air, 20 c.c. amounts of plain infusion broth were run in the air centrifuge tubes for five minutes. These were transferred to large test tubes after the addition of 5 per cent horse blood and incubated for eighteen hours at 37° C. They were examined for pneumococci and beta hemolytic streptococci. If these organisms were found, the same typing and grouping procedures were used as outlined above.

EXPERIMENTAL

The study was divided into four phases; namely, the determination of the effect of ultraviolet irradiation on (a) the number of air-borne organisms, (b) the character of these organisms, (c) subclinical hospital infections, and (d) clinical hospital infections. These phases were carried on simultaneously. However, before any routine could be set up for studying the first phase, a time for taking air samples had to be chosen that would be least variable from day to day. The air was sampled repeatedly during various activities in the ward throughout twenty-four-hour periods while the ultraviolet lamps were off. As seen in Table I, the bacterial counts throughout twenty-four hours were fairly stable except for periods of cleaning activities such as sweeping, dusting, making beds, and emptying baskets. Dry sweeping led to the highest increases in numbers of air-borne organisms, while other activities alone did not raise the counts as markedly. Late morning and afternoon samples gave the least variable results. Moderate variations in the number of patients present in the ward did not appear to influence the number of air-borne bacteria in these experiments. The recovery of alpha streptococci, an organism considered by some workers to be an index of human contamination of air, was small.

Since the numbers of organisms in the air were most stable in the late morning and afternoon, these times were selected for air sampling to determine the effect of ultraviolet light on the number of air-borne organisms. Central positions for sampling were chosen. During the experimental period the doors of the connecting corridor were open, a fact which was subsequently found to be significant in the outcome of these studies. Upon irradiation in the west wing, an average of thirty-eight organisms per 5 cu. ft. of air was obtained and the nonirradiated control ward showed sixty-six organisms per 5 cu. ft. of air. When the west wing was not irradiated, an average of 210 organisms was recovered from 5 cu. ft. of air, and in the east wing, 226 organisms. These results indicated that there was an exchange of air between the two wards with an effect on the number of air-borne organisms and a possible effect on the kinds of air-borne organisms and on subclinical and clinical cross-infections. This observation was verified by subsequent tests when the doors of the connecting corridor were closed and the

TABLE I

DETERMINATION OF THE QUANTITATIVE FLUX OF THE AIR-BORNE BACTERIAL FLORA THROUGHOUT A TYPICAL DAY IN THE WARD (ULTRAVIOLET LIGHTS OFF)

TIME	ACTIVITIES	I		II		III	
		TOTAL NO. OF ORGANISMS/SAMPLE*	NO. OF ALPHA STREPTOCOCCI	TOTAL NO. OF ORGANISMS/SAMPLE*	NO. OF ALPHA STREPTOCOCCI	TOTAL NO. OF ORGANISMS/SAMPLE*	NO. OF ALPHA STREPTOCOCCI
10:25 P.M.	Before ward rounds of nurses; feeding, fairly quiet	153	0.0	98	0.0	103	0.0
11:20 P.M.	After ward rounds of nurses; more activity	143	0.0	96	0.0	111	0.0
6:40 A.M.	Before ward rounds of nurses; moderate activity; baskets emptied	288	1.6	224	0.3	163	0.3
7:40 A.M.	Dry sweeping; weighing of children; active	1093	0.0	2134	0.3	536†	0.0
8:40 A.M.	Prior to intern rounds; children quiet—eating	846	0.0	915	0.3	431	0.0
10:10 A.M.	Directly after intern rounds; children fed; some coughing, crying	228	0.3	247	0.0	106	0.0
1:05 P.M.	Before doctors' rounds; some crying	157	0.0	194	0.0	98	0.0
2:45 P.M.	After doctors' rounds; active, small amount of crying	124	0.0	115	0.3	113	0.6
5:05 P.M.	Regular activities of feeding, changing diapers, etc.	116	0.0	124	0.0	121	0.0

*Sample = the average count of three tubes taken at a location.

†Dry sweeping was discontinued after the results of Experiments I and II were obtained.

west wing irradiated. A mean of nine samples revealed ten organisms per 5 cu. ft. of air in the irradiated and 100 organisms per 5 cu. ft. of air in the nonirradiated ward at the time the samples were taken.

Since the effect of the open corridor was not realized until the study was discontinued for the summer, this information could not be utilized in the studies reported here. In spite of this handicap, there was some effect on subclinical hospital infection. The spread of pneumococci in the irradiated and nonirradiated wards was studied. Unfortunately, typing sera for Group A hemolytic streptococci were not available.

As noted, the chief difference between the two wards is the installation of ultraviolet lamps above the entrance to the cubicles of the west wing. Irradiation was continuous. When admitting patients, those with upper respiratory and other diseases were distributed as evenly as possible. Swabbings were made of the nasopharynx and throat of all patients on admission, of all patients, nurses, internes and help once a week, and of any individual in those groups who showed clinical manifestations of a respiratory infection. This was done to determine the introduction and spread of the pneumococcus. The criterion for hospital infection was the appearance of a new organism in the nasopharyngeal and throat culture that had been absent for at least seven to ten days prior to the positive findings. If there was a reappearance of an organism fourteen days after the last positive culture, this was considered a continuation of the infection.

TABLE II

PNEUMOCOCCAL CROSS-INFECTIONS AMONG INFANTS OF THE IRRADIATED AND NONIRRADIATED WARD

	WEST WING (IRRADIATED)		EAST WING (NONIRRADIATED)	
	NO. OF PATIENTS	PER CENT	NO. OF PATIENTS	PER CENT
Total admissions	73		54	
Patients entering with upper respiratory infection	40	55	25	46
Patients admitted carrying pneumococci	20	27	16	29
Pneumococcal infections contracted in the hospital	14	19	18	33
Patients possibly infected by the air-borne route	5	7	9	17
Patients possibly infected by contact	3	4	4	7
Patients whose source of infection was unknown	6	8	5	9

During the period of observation, seventy-three patients were admitted into the irradiated ward and fifty-four into the control ward. Table II shows the distribution of pneumococci among new admissions and the number of bacterial infections subsequently acquired. As can be seen, forty (55 per cent) of the patients entering the irradiated ward and twenty-five (46 per cent) of those entering the control ward had an upper respiratory infection. Of these, twenty (27 per cent) in the irradiated and sixteen (29 per cent) in the control wing were admitted carrying pneumococci. Pneumococcal hospital infections were found in fourteen (19 per cent) of the patients in the irradiated ward and eighteen (33 per cent) of those in the nonirradiated ward. Since the pneumococci could be typed, it was possible tentatively to determine the route of infections. It appeared that five out of seventy-three (7 per cent) of the patients in the irradiated ward and nine out of fifty-four (17 per cent) of those in the nonirradiated ward were possibly infected by the air-borne route, since during the time in question the particular

type of pneumococcus was not isolated from any member of the ward personnel but only from other patients with whom there were no close contacts. Infection by contact was assumed in three patients (4 per cent) in the west wing and four patients (7 per cent) in the east wing, because the corresponding organisms were harbored by nurses attending these patients. In six patients (8 per cent) in the irradiated wing, and five patients (9 per cent) in the nonirradiated wing, the bacterial infection could not be traced. It is obviously impossible in such a study to substantiate these assumed routes of cross-infection.

Throughout the test period, few clinical cross-infections occurred in either the irradiated (three cases) or nonirradiated (four cases) wards. There also was little difference between the number of pathogenic organisms isolated from the air of the two wards. Of ninety samples taken in the irradiated ward, thirty-six were positive for hemolytic streptococci, and of sixty-seven samples from the nonirradiated ward, thirty-four showed similar organisms. Pneumococci were isolated from only 1 out of 157 samples. These facts again pointed to the possible role of the open corridor.

DISCUSSION

The facts that there were few clinical cross-infections throughout the test period and that the number of pathogenic bacteria recovered from the air of irradiated and nonirradiated wards were so similar pointed to the possibility of an exchange of air between the two wards through the open corridor. This was substantiated by air samples. Since the experimental and control wards at The Children's Hospital of Boston also are connected by an open corridor, this might be a factor toward possibly explaining the discrepancies between the findings of del Mundo and McKhann[6] and those of Brooks[18] in the following year.

Although the observations of some workers clearly show the effectiveness of ultraviolet irradiation as a source of air disinfection,[6, 16, 17] several uncontrollable factors in a hospital experimental set-up remain. The route of infection can seldom be absolutely proved and frequently cannot be indicated. In our own experiment, although the bacterial flora of patients, nurses, interns, and help were carefully followed, organisms could still have been missed. It was found impossible, moreover, to study the respiratory organisms of the staff and visiting physicians, of the medical students, or of the few visitors permitted entrance to the wards. Furthermore, children had to be removed from their cubicles to treatment rooms, x-ray department, and other localities. Differences in susceptibility and exposure are important variables. All these factors tend to make the interpretation of such studies difficult. Finally, the amount of effort, time, and cost involved were considerably greater than the returns warranted.

For future study of the problem, it is considered highly desirable to divide the approach so as to study one mode of air-borne infection at a

time in order to obtain basic understanding of the routes involved. This knowledge may then be used to interpret the findings from more complex situations. Animal studies with known organisms would do much to simplify the investigation and permit controlled experiments. Such experiments are reported in another paper.[22]

CONCLUSIONS

1. Ultraviolet light was found to be effective in reducing the number of air-borne organisms in a hospital ward.

2. An open connection between the irradiated and nonirradiated ward had some effect in reducing the number of air-borne organisms, and possibly influenced the kinds of air-borne organisms and the number of subclinical and clinical hospital infections in the nonirradiated ward.

3. There was a suggestive difference between the number of pneumococcal cross-infections contracted in the irradiated and control wards.

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STUDIES ON AIR-BORNE INFECTION IN A HOSPITAL WARD

II. Effects of Ultraviolet Irradiation and Propylene Glycol Vaporization Upon the Prevention of Experimental Air-Borne Infection of Mice by Droplet Nuclei

Werner Henle, M.D., Harriet E. Sommer, and Joseph Stokes, Jr., M.D., Philadelphia, Pa.

IN A preceding communication results have been presented of a study comparing air-borne hospital infections among infants on a ward protected by ultraviolet irradiation and on a similar control ward.[1] Although in this case, as in some others,[2, 3, 4, 5] ultraviolet irradiation appeared to reduce the incidence of hospital-acquired air-borne infections, many factors tend to interfere with the correct interpretation of the results, such as differences in individual exposure, susceptibility, and response of infants. Tracing of the responsible organisms through the air will frequently fail, and other routes of infection may not be excluded. Furthermore, the number of clinical and bacteriologic hospital infections of the respiratory tract was small, partly due to the success of the sulfonamides in early elimination of foci of infection.

The scanty data obtained in the clinical study are in striking contrast to the amount of time and material spent on the problem. It was, therefore, thought that animal experimentation on the ward under controlled conditions might give more reliable information in a shorter period of time. It is the purpose of this paper to present results of experiments concerning the disinfection of air which has been artificially contaminated with droplet nuclei derived from cultures of hemolytic streptococci of Lancefield's group C or the virus of influenza A.* Experimental air-borne transmission of both organisms to mice has been studied before.[7, 8] In the present studies the effectiveness of ultraviolet irradiation has been compared with that of propylene glycol vapor as an air disinfectant. Propylene glycol vapor alone was first used by Robertson and his associates[9] for the destruction of air-borne bacteria and was also found effective against the virus of influenza A.[10, 11]

From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and The Children's Hospital of Philadelphia.

*It should be pointed out that respiratory infection may be spread by any one of three ways: (1) by direct hits of Flügge droplets, (2) by the inhalation of infected dust, or (3) of infected droplet nuclei, the floating residue of small droplets after evaporation. Adequate information as to the importance of each is missing. Specific measures are required to prevent the spread of respiratory infection by these various ways (Andrewes).[6] The present study is concerned only with the protection against infection by droplet nuclei.

METHODS AND MATERIALS

Ward.—The ward, measuring 47 by 27 by 11 feet and having a volume of roughly 14,000 cubic feet, has been described in Part I* of this study. The sixteen separate cubicles were evacuated and only bedframes and tables left in their usual position. All connections to other wards were sealed and the windows and doors kept closed during experimentation. A fan with a fourteen-inch blade and rotating at an angle of 90° was used to produce some movement of air. In order to

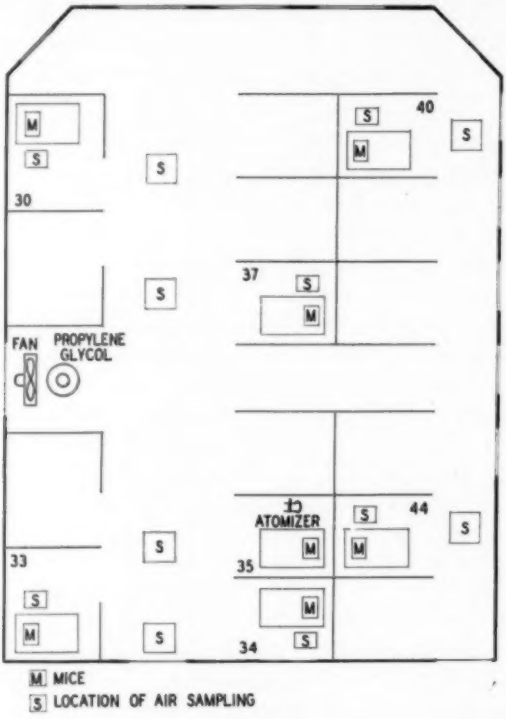

Fig. 1.

show the various arrangements and test locations used in this study, a floor plan is given in Fig. 1. Cubicle 35 was chosen as the infector cubicle containing the atomizer, since all possible routes of cross-infection could be traced from here. The following cubicles were selected for testing: 34, to the left side of the "infector cubicle"; 33, opposite; 44, in the rear; 30 and 40, farthest away from the atomizer; and 37, in the middle of the ward.

β Hemolytic Streptococcus.—Six-hour cultures of a highly virulent streptococcus of Lancefield's Group C, originally isolated from an epi-

*Part I appears on p. 569 of this issue.

demic of lymphadenitis in guinea pigs, were used. The strain was passed through mice shortly before each experiment and grown in blood broth. The culture fluid was carefully removed from the flasks, leaving most of the settled blood, and atomized without further treatment.

A threefold titration of the culture was carried out in the early experiments by intra-abdominal and intranasal inoculation of mice and by plating. Tenfold dilutions of the six-hour cultures were made and three mice each inoculated intra-abdominally with 0.5 ml. of the different dilutions, or intranasally under light ether anesthesia with 0.05 ml. Pour plates were made in duplicate for each dilution; one set was inoculated with 0.5 ml. and the other with 0.05 ml. Since there was constant agreement between intranasal and intra-abdominal titration, and one to ten organisms per mouse proved fatal by either route (usually 10^{-9} and 10^{-8} respectively), only intra-abdominal titrations were carried out in later experiments.

Influenza Virus.—The extra-embryonic fluid of the chick infected with influenza A was used as the source of the virus. Ten-day-old embryos were inoculated into the allantoic sac with 0.5 ml. of a suitable dilution of fluid, as described elsewhere,[12] and incubated at 39° C. for from twenty-four to forty-eight hours, when the allantoic and amniotic fluids were harvested. The forty-second passage of the PR-8 strain[13] and the thirty-fourth passage of the F-12 strain[14] of influenzal A virus were employed. The fluids were kept at –15° C. until used.

Atomizer.—For the atomization of the cultures, an arrangement was used similar to that described and explained in detail by Wells and Lurie.[15] The atomizer itself was inserted through the sidearm into the atomizer flask by means of a rubber stopper. It consisted of an 18-gauge needle, pushed through the stopper, with a 50 ml. Yale syringe adapter suspended by a rigid wire over its tip with the wide opening pointing upward. A 1 ml. syringe barrel was attached to the needle and connected by pressure tubing to a compressed air tank. The atomizer operated at a pressure of twenty-six pounds with 0.33 cubic foot of air passing through per minute. This arrangement proved to be fairly stable and consistent.

Atomization of culture continued over the whole period of an experiment unless otherwise stated. When using streptococci the culture in the spray flask was replaced every hour by organisms which had been kept in the refrigerator for not more than two hours, during which time no drop in the number of viable bacteria occurred. For experiments extending over a longer period of time, blood broth was seeded at various times so as to yield six-hour cultures at the desired intervals. In the case of influenza virus, fresh fluid was added from time to time to the flask during any one experimental period, and complete changes were made only for each new phase.

Mice.—Four- to five-week-old Swiss white mice weighing from 12 to 15 Gm. were used as test animals. During exposure to the air-borne

organisms they were kept in wire-mesh cages to insure free circulation of air. The cages were placed on the bed frames within the cubicles in such a manner that they were not subjected to direct ultraviolet irradiation. Freshly disinfected cages were used for each group of mice. The experimental animals were exposed in groups of ten to the contaminated air for 150 minutes usually, and only in one instance for double this period.

All mice found dead after exposure to air-borne streptococci of Lancefield's group C were autopsied and examined for pulmonary lesions. Cultures were taken from the lung and frequently from the heart's blood when indicated. Surviving mice were sacrificed on the eighth or tenth day, with two exceptions. The lungs and heart's blood were studied bacteriologically and lesions recorded. In the two exceptional cases, surviving mice were inoculated on the eighth or tenth day with a suspension of influenzal A virus or sterile broth by the intranasal route under light ether anesthesia (0.05 ml.) for the identification of streptococcal carriers, as will be explained in the text.

All mice exposed to the air-borne influenzal A virus that died within the experimental period were inspected for typical pulmonary lesions. Surviving mice were autopsied on the eleventh or twelfth day and the degree of lung involvement recorded in the usual manner: 4 = complete consolidation; 1 – 3 = various degrees of involvement; 0 = apparently normal lungs.

Air-Sampling.—Twenty-four hours before each experiment the ultraviolet lights in the ward were turned on to reduce the number of air contaminants as far as possible. Sampling of the air was carried out by two means: the Wells air centrifuge and exposure of blood agar plates.

The centrifuge was run for three minutes, during which time 4.4 cubic feet of air passed through the instrument. Although this short time of sampling markedly decreased the accuracy of the method, longer runs were not found feasible on account of the high concentrations of air-borne streptococci encountered, which resulted in extreme density and confluence of the colonies in the centrifuge tubes. The percentage of organisms recovered, therefore, will be lower than under standard conditions, and the tube counts may be used only for comparing the various experiments of this study.

Two centrifuges were available for most of the experiments. The samples were taken at a height of approximately five feet from the floor, at locations indicated in Fig. 1. Tryptose phosphate blood agar served as the medium. All specimens were incubated at 37° C. for from eighteen to twenty-four hours and counted according to standard technique.[16]

Agar plates containing 7.5 per cent horse blood were placed directly in front of the mouse cages on the bed frames and on the table in the

corridor. They were exposed for five minutes and the number of colonies counted after incubation at 37° C. for from eighteen to twenty-four hours.

Ultraviolet Lights.—General Electric eighteen-inch germicidal lamps served as the source of ultraviolet irradiation. They were installed in such a manner that three curtains of ultraviolet light were formed, one covering the open front of the cubicle and two spread horizontally over the cubicle and corridor, as demonstrated in Fig. 2 of the preceding paper. The efficiency of the lamps was checked at frequent intervals and replacements made when necessary.

Propylene Glycol Vapor.—Propylene glycol* was vaporized from a graduated enamel container placed on a hot plate in front of the fan, as indicated in Fig. 1. This set-up insured rapid dispersion of the vapor, but it is not easily controllable, and development of techniques for uniform experimentation is desirable. An accurate method for determining the concentration of propylene glycol in air has been reported only recently by Puck,[17] when this study was already terminated. Approximate values have been calculated from the volume of the agent vaporized into the air of the ward (14,000 cubic feet). However, these calculations do not take into account losses due to leakage of air, precipitation of the agent, etc. Extensive precipitation of propylene glycol was noted only once in these experiments, when a total of 700 ml. had been vaporized during a period of three hours. When 400 ml. were used during a similar interval, no such effect was noted.

The concentrations of propylene glycol used in all of the experiments herein recorded ranged, as far as could be determined, somewhere between 1:2,000,000 and 1:5,000,000, with the exception of one experiment in which precipitation of the propylene glycol occurred.

EXPERIMENTAL

Preliminary Experiments.—In preliminary experiments it was found that atomization of a culture of streptococci of Lancefield's Group C led to a rapid spread of this organism throughout the air of the ward (Table I). After a linear increase in concentration of the air-borne bacteria during the first forty-five to sixty minutes, a stage was reached during which the number of streptococci per cubic foot of air remained roughly constant. Since the atmosphere was not quiet and air currents were produced by the fan as well as by the movements of the workers, variations such as encountered in this experiment could be expected. Repetition of this experiment with the same culture kept at 4° C. for 150 minutes gave nearly identical results.

When the final concentration of organisms recovered from one cubic foot of air under control conditions was roughly under 1,000, few, if any, air-borne streptococci were found in either cubicle or corridor

*Eastman Kodak Co.

under the influence of ultraviolet irradiation using the same culture for atomization. However, if, in the controls, the number of bacteria sedimented from one cubic foot of air was uncountable (certainly more than 3,000 organisms), an appreciable number of streptococci escaped through the ultraviolet light barriers into the air of cubicles adjacent to the one containing the atomizer, but the count decreased with increasing distance from the source of infection and correspondingly repeated chance of exposure to irradiation. Propylene glycol vapor, on the other hand, was effective in disinfecting the heavily contaminated air, even close to the atomizer. Protocols pertaining to these points are included in Tables III and IV.

TABLE I

SPREAD OF AIR-BORNE STREPTOCOCCI OF LANCEFIELD'S GROUP C THROUGHOUT THE WARD UNDER CONTROL CONDITIONS

TIME AFTER ONSET OF BACTERIAL ATOMIZER IN MINUTES	NUMBER OF ORGANISMS RECOVERED FROM 1 CUBIC FOOT OF AIR IN CUBICLE					
	33	44	34	37	30	40
0 to 15	507	573	922	587	873	999
30 to 45	1,209	985	1,912	Sp.	Sp.	Sp.
45 to 60	1,833	2,230	Sp.	3,534	4,785	4,561
90 to 105	1,614	1,970	2,075	Sp.	Sp.	2,480
120 to 135	1,851	2,138	Merg.	1,481	2,347	Sp.
150 to 165	1,439	2,718	1,691	2,906	2,067	Sp.
240 to 255	2,012	3,270	2,040	3,241	1,852	1,726

Sp. = Spreader.
Merg. = Merging colonies.

The determination of the time of survival and the rate of settling of air-borne streptococci gave results closely comparable to those obtained by Wells and Fair[18] and Robertson and her associates[19] with other organisms. The normal settling and dying off proceeded at such a rate that at the end of three hours appreciable numbers of streptococci were still suspended in the air. Ultraviolet irradiation reduced the concentration of air-borne organisms by more than 99 per cent within ten minutes and no streptococci were cultured after twenty minutes. One experiment conducted with propylene glycol vapor gave results between these extremes, since some time passed until a sufficient concentration of this agent had been reached to destroy the suspended organisms in air.

While discontinuation of irradiation causes immediate loss of protection, propylene glycol vapor remains active for some time after evaporation has ceased. Table II demonstrates that after 250 ml. of propylene glycol had been vaporized, air centrifuge tubes and blood plates showed no or relatively little growth for the following fifty to sixty minutes. In control experiments such as those shown in Table I, on the other hand, large numbers of organisms were recovered very shortly after onset of atomization from the air in the far off cubicles (30 and 40).

TABLE II

PERSISTENCE OF THE EFFECT OF PROPYLENE GLYCOL VAPOR ON AIR-BORNE STREPTOCOCCI (GROUP C)

TIME IN MINUTES	PROPYLENE GLYCOL	BACTERIAL ATOMIZER	CUBICLE 34		CUBICLE 40	
			ORGANISMS IN 1 CUBIC FOOT OF AIR	ORGANISMS SETTLING IN FIVE MINUTES	ORGANISMS IN 1 CUBIC FOOT OF AIR	ORGANISMS SETTLING IN FIVE MINUTES
0	On					
45 to 55	On	On	0	0	0	0
56 to 65	On	On	0	0	0	0
65	Off (250 ml.)					
0 to 10		On	0	0	0	0
11 to 20		On	0	0	0	0
21 to 30		On	3	6	0	0
31 to 40		On	33	15	3	0
41 to 50		On	52	18	6	0
51 to 60		On	N. C.	296	11	2
91 to 100		On	N. C.	440	1,800	192
121 to 130		On	N. C.	2,160	N. C.	424
181 to 190		On	N. C.	N. C.	N. C.	1,924
241 to 250		On	N. C.	N. C.	N. C.	1,954
250		Off				

N. C. = Not countable (more than 3,000 organisms per cubic foot of air).

Animal Experiments.—As a result of preliminary experiments, the following procedure was adopted for the comparison of the effectiveness of ultraviolet irradiation and propylene glycol vapor in preventing air-borne infection. During the first period of an experiment, groups of ten mice each were exposed in the various test cubicles to contaminated air irradiated by ultraviolet light. After two and a half hours, atomization of the culture was discontinued, but irradiation went on for ten minutes more before the control period was begun. During this second phase of the experiment new groups of mice were exposed for two and one-half hours to nontreated contaminated air. This was followed by irradiation of the air for forty minutes and vaporization of propylene glycol for thirty minutes prior to the onset of the third period. Thus complete disinfection of the air as well as a sufficient concentration of propylene glycol vapor was obtained before new groups of mice were exposed to contaminated air treated by this agent. Titration of the cultures at the onset of each phase gave nearly identical bacterial counts, indicating that conditions were closely comparable during the various periods.

When white mice were placed in the different test cubicles under the various conditions and exposed to *heavy* concentrations of air-borne streptococci of Group C, the effectiveness of ultraviolet irradiation or of propylene glycol vapor in preventing air-borne infection was obvious (Table III). Under control conditions the centrifuge tubes yielded innumerable colonies in all locations. Plate counts varied between 2,500 and 5,300 organisms. When propylene glycol was vaporized,

TABLE III

EFFECT OF ULTRAVIOLET LIGHT OR PROPYLENE GLYCOL VAPOR ON HIGH CONCENTRATIONS OF AIR-BORNE STREPTOCOCCI (GROUP C)

(A)

CUBICLE	NUMBER OF ORGANISMS RECOVERED FROM 1 CUBIC FOOT OF AIR (90 TO 120 MINUTES AFTER ONSET)			NUMBER OF ORGANISMS SETTLING OUT IN FIVE MINUTES (90 TO 120 MINUTES AFTER ONSET)		
	CONTROL	ULTRAVIOLET LIGHT	PROPYLENE GLYCOL	CONTROL	ULTRAVIOLET LIGHT	PROPYLENE GLYCOL
30	N. C.	8	0	2,496	4	0
33	N. C.	1,171	1	4,784	548	1
34	N. C.	1,819	2	5,316	672	0
37	N. C.	419	0	3,088	15	0
40	N. C.	12	0	4,524	0	0
44	N. C.	58	0	2,784	1	0

(B)

CUBICLE	MORTALITY IN MICE		
	CONTROL	ULTRAVIOLET LIGHT	PROPYLENE GLYCOL
30	$+\ +\ +\ +\ +\ +\ +\ +\ +$ $D_3D_4D_4D_4D_4D_4D_4D_5D_6$	S S S S S S S S S S	S S S S S S S S S S
33	$+\ +\ +\ +\ +\ +\ +\ +$ $D_3D_4D_4D_4D_4D_4D_4D_5SS$	S S S S S S S S S S	S S S S S S S S S S
34	$+\ +\ +\ +\ +\ +\ +\ +\ +\ +$ $D_3D_3D_3D_3D_3D_4D_4D_4D_4D_4$	S S S S S S S S S S	S S S S S S S S S S
35 (Atomizer)	$+\ +\ +\ +\ +\ +\ +\ +\ +$ $D_3D_3D_3D_4D_4D_4D_4D_5D_7S$	$+\ +\ +\ +\ +\ +$ $D_3D_3D_4D_4D_4D_5SSSS$	S S S S S S S S S S
37	$+\ +\ +\ +\ +\ +\ +$ $D_3D_3D_3D_4D_4D_4D_5SSS$	S S S S S S S S S S	S S S S S S S S S S
40	$+\ +\ +\ +\ +\ +\ +\ +$ $D_3D_4D_4D_4D_5D_5D_5D_9D_9S$	S S S S S S S S S S	S S S S S S S S S S
44	$+\ +\ +\ +\ +\ +\ +\ +\ E$ $D_3D_3D_3D_4D_4D_5D_5D_5D_6S$	S S S S S S S S S S	S S S S S

N. C. = Not countable (more than 3,000 organisms per cubic foot of air).
D_3 = Mouse died on third day.
S = Mouse survived ten days.
+ = Hemolytic streptococcus recovered from lung.
E = Eaten, no culture possible.

TABLE IV

EFFECT OF ULTRAVIOLET LIGHT ON LOW CONCENTRATIONS OF AIR-BORNE STREPTOCOCCI (GROUP C)

CUBICLE	NUMBER OF ORGANISMS RECOVERED FROM 1 CUBIC FOOT OF AIR		NUMBER OF ORGANISMS SETTLING OUT IN FIVE MINUTES		MORTALITY IN MICE	
	CONTROL	ULTRAVIOLET LIGHT	CONTROL	ULTRAVIOLET LIGHT	CONTROL	ULTRAVIOLET LIGHT
30	394	0	57	0	0	0
33	383	0	69	5	0	0
34	220	0	54	0	0	0
35 (Atomizer)	–	–	–	–	0	0
37	475	1	46	0	0	0
40	453	0	38	0	0	0
44	348	0	54	0	0	0

only very few colonies of the streptococcus were recovered both by the centrifuge and the plate method. Ultraviolet irradiation gave results somewhat between these extremes, higher tube and plate counts being encountered in locations close to the atomizer (cubicles 33 and 34 with 1,819 and 1,171 organisms, respectively, per cubic foot), while in the distant cubicles only relatively few streptococci were found. The results obtained in mice exposed to the air-borne organisms under these conditions follow the bacteriologic findings closely. With a few exceptions, the mice succumbed to streptococcal pneumonia and septicemia under the control conditions. When propylene glycol was vaporized, none died from streptococcal infection, not even in the cubicle containing the atomizer. Ultraviolet irradiation prevented death of the mice in all but one location, the "infector" cubicle, where six of the ten mice died. Although high concentrations of organisms were found in other cubicles in spite of ultraviolet irradiation, all remaining mice survived. However, in another experiment more than 3,000 streptococci were counted in cubicle 33, in spite of the ultraviolet light barriers. In this case some of the exposed mice succumbed to streptococcal infections.

In earlier experiments mice were exposed to *lower* concentrations of air-borne streptococci with no resulting mortality, and bacteriologic examination of the lungs and heart's blood on the eighth day usually proved negative for this organism. However, successful aerial transmission of the streptococcus under such conditions could be demonstrated in other experiments by provocative infection with the virus of influenza A or occasionally, too, by the simple expedient of intranasal instillation of sterile broth eight to ten days after exposure to the contaminated air. An experiment of this type is exemplified in Tables IV and V. It is shown that when 220 to 475 organisms per cubic foot of air were found in the various test locations under control conditions, and plate counts yielded forty-six to fifty-seven colonies, ultraviolet irradiation almost completely sterilized the air (propylene glycol was not used in these experiments). All mice but one survived the exposure to a low concentration of air-borne streptococci, and this one succumbed to an intercurrent disease (Table IV). On the eighth day the mice previously exposed to the contaminated air under control conditions and those having inhaled the irradiated air were divided into two equal groups and the influenzal A virus or sterile broth was injected intranasally under light ether anesthesia. As seen in Table V, all mice infected with the influenza virus died within three to seven days with typical influenzal lesions. Cultures of the lungs or heart's blood now yielded hemolytic streptococci of Lancefield's Group C from practically all animals belonging to the control group, while only three mice of the "irradiated group" revealed streptococcal colonies. These animals came from the cubicle where the culture was atomized. Instillation of sterile broth led to the death of five mice in the control group, four of which harbored

the streptococcus, while only one died in the "irradiated group" without bacteriologic findings. No streptococci could be isolated from the surviving mice when autopsied on the tenth day after the inoculation of broth; i.e., the eighteenth day after the exposure to the air-borne streptococcus.

TABLE V

INTRANASAL INOCULATION OF STERILE BROTH OR INFLUENZA VIRUS INTO MICE EIGHT DAYS AFTER EXPOSURE TO SUBLETHAL CONCENTRATIONS OF AIR-BORNE STREPTOCOCCI (GROUP C)

CUBICLE	MORTALITY IN MICE PREVIOUSLY EXPOSED TO			
	IRRADIATED AIR		NONIRRADIATED AIR	
	BROTH	INFLUENZA VIRUS	BROTH	INFLUENZA VIRUS
30	S S S S S – – – –	$D_2D_2D_2D_2S$ – – – –	+ + D_2D_2S S S	+ + + + + $D_2D_2D_2D_4D_5$
33	S S S S S – – – – –	$D_2D_2D_2D_2S$ + +	S S S S S $D_2D_2D_2D_5D_5$	+ + + + + + + + + +
34	S S S S S –	$D_2D_2D_2D_2D_5$ – – + + +	D_2D_2S S S $D_2D_2D_2D_2D_6$	+ + + + + + + + + +
35 (Atomizer)	D_2S S S S – – – – –	$D_2D_2D_2D_2D_7$ – – – – –	S S S S S $D_2D_2D_2D_2D_5$	+ + + + + + + + + +
37	S S S S S – – – – –	$D_2D_2D_4D_4D_5$ – – – – –	S S S S S –	$D_2D_2D_2D_2D_6$ + + + + +
40	S S S S S – – – – –	$D_2D_2D_2D_4D_5$ – – – – –	D_2S S S S $D_2D_2D_2D_2D_5$	$D_2D_4D_4D_5D_5$ + + + + +
44	S S S S S	$D_2D_2D_4D_5D_5$	S S S S S	$D_4D_4D_4D_5D_5$

D_2 = Mouse died on third day.
S = Mouse survived ten days.
+ = Streptococcus recovered.
– = Streptococcus not recovered.

TABLE VI

EFFECT OF ULTRAVIOLET LIGHT AND PROPYLENE GLYCOL VAPOR ON AIR-BORNE INFLUENZA VIRUS

CUBICLE	MORTALITY AND LESIONS IN MICE		
	CONTROL	ULTRAVIOLET LIGHT	PROPYLENE GLYCOL
30	$D_7D_7D_7D_7D_5D_5D_5D_5D_5D_5$	0 0 0 0 0000000	0000000000 D_6* E
33	$D_7D_7D_7D_7D_7D_7D_7D_5D_5D_5$	2 1 1 1111000	0000000000 D_7*
34	$D_6D_7D_5D_5D_5D_5D_{10}D_{10}D_{10}$	2 2 1 1100000	0000000000
35 (Atomizer)	$D_5D_5D_5D_6D_6D_6D_7D_5D_5D_5$	$D_7D_5D_5$ 3 3 3 2 2 1 1	3 3 1 0 0 0 0 0 0 0
37	$D_6D_7D_7D_7D_7D_7D_7D_5D_5D_5$	0 0 0 0 0000000	0000000000
40	$D_7D_7D_7D_7D_7D_7D_7D_8D_5D_5$	0 0 0 0 0000000	0000000000 D_6*
44	$D_7D_7D_7D_7D_7D_7D_5D_5D_5D_5$	0 0 0 0 0000000	0000000000

D_5 = Mouse died on fifth day.
1-3 = Degree of pulmonary consolidation on tenth day.
*Atypical death.
E = Eaten, not autopsied.

This observation necessitated the testing of mice surviving exposure to heavily contaminated air treated by either ultraviolet irradiation or by propylene glycol vapor by such provocative inoculation of the influenza virus. The experiment recorded in Table III was followed up in this way. All surviving mice were inoculated intranasally with approximately 1,000 M.L.D. of the PR-8 strain of influenza A, leading to their death within five to ten days. The few animals left from the

control group all harbored the streptococcus, while in the "propylene glycol group" all cultures were negative, and only three out of sixty mice in the "irradiated group" yielded streptococcal colonies, in spite of relatively high bacterial counts in some of the cubicles close to the atomizer at the time of exposure to the air-borne streptococcus.

In another series of experiments, mice were exposed to the air-borne virus of influenza A under conditions similar to those described for the streptococcus. As seen in Table VI, all control mice died within ten days after the exposure to the virus, with typical pulmonary involvement. Of the mice exposed during ultraviolet irradiation in this and two similar experiments, the only deaths and major lesions occurred in the cubicle containing the atomizer (35). The animals in cubicles 33 and 34, which were close to the atomizer, showed lung lesions in a number of instances, but no death occurred. The mice in all other locations were apparently normal. Propylene glycol vapor in this, as in the streptococcal experiment, gave even higher protection, in that only three mice in the "infector" cubicle showed influenzal lesions on the twelfth day, and only two of these were marked. Three deaths occurred from intercurrent infections.

DISCUSSION

From the various experiments conducted with the streptococcus of Lancefield's Group C, it was obvious that the concentration of air-borne organisms had to be fairly high in order to produce death in the exposed mice. No accurate figure can be given on account of the fact that the colonies in the air centrifuge tubes in the control experiments usually were uncountable, but it appears certain that at least 3,000 streptococci per cubic foot of air were required for the length of the exposure. This figure probably is too low, since analysis of the efficiency of the centrifuge has shown that only a certain percentage of the suspended organisms can be recovered.[20, 21] On the other hand, a mouse inhaled probably not more than one-twentieth of a cubic foot of air during the experimental period, assuming consumption of about 10 ml. of air per minute per animal.[22] The relationship between fresh air and tidal air, however, is unknown, and so is the degree of retention of air-borne organisms within the respiratory tract. These considerations tend to counteract the error in the air centrifuge results. Disregarding these sources of error, inhalation of 150 to 200 air-borne streptococci of this strain must be considered as lethal for mice.

When a streptococcal culture or dilutions thereof was instilled intranasally under light ether anesthesia, as few as one to ten organisms were found to be fatal for mice. Analysis of the discrepancy between this route of inoculation and the exposure to air-borne streptococci requires further experimentation. It may be that a few organisms suspended in broth and incubated within the lung may rapidly multiply

and exert their lethal effect while the infected droplet nuclei falling on a relatively dry surface may not find optimal conditions.

As few as 250 streptococci per cubic foot of air were sufficient to induce a carrier state in the mouse, as shown by subsequent inoculation of the virus of influenza A. According to the rough calculations above, not more than ten organisms may have been inhaled per mouse. The role of this carrier state in a subsequent influenzal infection has not as yet been determined. The dose of influenzal virus used might have been too large (1,000 to 10,000 M.L.D.) to reveal any differences between the normal mice and the streptococcal carriers. A smaller dose or even a sublethal inoculum might have given different mortalities, a point which remains to be investigated.

Mice exposed to much higher concentrations of air-borne streptococci surviving irradiation by ultraviolet light (1,100 to 1,800 organisms per cubic foot) gave different results. Only very few out of the total number of mice became carriers, and the loss of certain streptococcal properties due to this agent has been suspected. Such changes have been noted by Wells and Lurie[15] in air-borne tubercle bacilli surviving irradiation in that the disease in rabbits following inhalation of these organisms was less rapidly fatal than that produced by an equal number of nonirradiated bacilli. Retardation of the lag phase of some organisms was noted by Hollaender and Duggar[23] and by Rentschler, Nagy and Mouromseff[24] as the result of exposure to ultraviolet light, and Sharp[25] reported that certain chromobacteria lost their ability to form pigment by such treatment. It seems, therefore, that although organisms may pass the ultraviolet light barriers in appreciable numbers, they nevertheless may have been sufficiently altered to diminish the danger of air-borne infection. This point needs further analysis.

Ultraviolet irradiation thus prevented not only fatal infection in mice but also the establishment of carriers to a large extent. The only exceptions were found in mice originally placed in the infector cubicle. In this case, organisms could pass to the experimental animals without exposure to the ultraviolet rays. Propylene glycol vapor, on the other hand, sterilized the air completely and even in this location no fatal infection nor the inducement of a carrier state occurred.

Technical equipment for ultraviolet irradiation has been developed to such a point that it can be applied easily to practical problems. Quantitative techniques for the vaporization of propylene glycol, on the other hand, are in the experimental stage. A test for the determination of propylene glycol in air, recently described by Puck[17] has to be applied to these problems in order to keep the concentration of the agent in its effective range. The saturation point is reached when 0.7 mg. has been vaporized in one liter of air, corresponding to a dilution of 1 in 1.4 million.[9b] It did not disinfect the heavily contaminated air in a dilution of one in ten million, under the conditions of these experiments.

As has been pointed out, this study was devoted to the destruction of infected droplet nuclei in concentrations far in excess of what might be encountered under ordinary conditions. There is no apparent reason why ultraviolet irradiation or propylene glycol vapor should not be similarly effective in preventing epidemic outbreaks of respiratory infection among human beings, provided the spread is accomplished by droplet nuclei. Definite evidence for this contention has been recently presented by Wells, Wells and Wilder[26] concerning the prevention of measles, mumps, and chicken pox in schools near Philadelphia by ultraviolet irradiation of classroom air. Direct hits by Flügge droplets and possibly dust-borne infections require different preventive measures.

SUMMARY

Experiments have been reported on the prevention of air-borne infection in white mice, conducted in a large hospital ward (14,000 cubic feet) subdivided into sixteen separate cubicles. Groups of animals were placed in some of the locations, while cultures of the hemolytic streptococcus of Lancefield's Group C or of the virus of influenza A were atomized in one of the cubicles. Both organisms spread rapidly throughout the air of the ward. Ultraviolet irradiation and propylene glycol vapor were compared in their effectiveness as disinfectants of the air.

With *heavy* concentrations of air-borne streptococci (more than 3,000 cells per cubic foot of air) most of the control mice died from streptococcal pneumonia and septicemia, while propylene glycol vapor protected them completely and ultraviolet irradiation failed to prevent death only in the cubicle containing the atomizer.

With *low* concentrations of the streptococcus (200 to 500 organisms per cubic foot of air), all mice survived and cultures taken from the lungs on the eighth or tenth day failed to reveal the streptococcus. However, it could be shown in other experiments that a carrier state had been induced in the animals exposed under control conditions, and not in those protected by ultraviolet light barriers. This was demonstrated by inoculation of the virus of influenza A eight to ten days after exposure to the air-borne streptococcus. All mice died from influenza, but only those belonging to the control group now showed hemolytic streptococci in cultures taken from the lungs. Instillation of sterile broth only occasionally activated the streptococcus in the carrier.

Ultraviolet irradiation and propylene glycol vapor were similarly effective in preventing the air-borne infection with the virus of influenza A. While all control mice succumbed to the disease, propylene glycol vapor protected the animals completely against death and only a few lesions were noted in animals from the cubicle containing the atomizer. More lesions and several deaths were observed in the same cubicle when

the air was irradiated by ultraviolet lights, and pulmonary involvement was noted also in other locations close to the atomizer, under the same conditions.

These results indicate that both ultraviolet light and propylene glycol vapor are effective disinfectants of the air. Their application will depend upon the individual problems and the location to be disinfected. It must be re-emphasized that only infection by droplet nuclei has been studied. Flügge droplet and possibly dust-borne infections may require different means of control.

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DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY

II. Hemolytic Streptococcal Meningitis

Alexis F. Hartmann, M.D., Dorothy Wolff, Ph.D.,
Frances M. Love, M.D., and Barbara S. Kendall
St. Louis, Mo.

DURING the period since the first case of meningitis was treated with sulfonamides in the St. Louis Children's Hospital and the time of this writing (approximately five years), the patients admitted with signs and symptoms sufficiently suggestive of bacterial meningitis to demand special investigation with such a diagnosis foremost in mind and to suggest sulfonamide drug administration pending accurate diagnosis as to the type of infection numbered approximately 100 and are summarized in Table I. All cases managed by the pediatric service or by the department of otolaryngology with pediatric supervision, particularly in regard to treatment, are included.

We have decided to review first our twelve cases of acute hemolytic streptococcal meningitis. In the great majority of cases, such infections are the result of extension of otitis media, mastoiditis, or petrositis and from the beginning are joint problems of the pediatrist or internist and the otolaryngologist, with much help expected from the bacteriologic laboratory and the x-ray department, just as were the cases of lateral sinus phlebitis reported in the first paper of this series.[1]

REPORT OF CASES RECOVERING

Case 1 (Chart 1, and Table II).—This boy, L. W., aged 20 months, developed an upper respiratory infection on Dec. 5, 1936. Three days later an area of cellulitis was seen on his left leg, and on Dec. 11 a stiff neck was noted. On Dec. 12 the initial hospital examination confirmed the presence of cellulitis and suggested an associated septicemia and possible meningitis. The blood culture grew hemolytic streptococci. A spinal tap, however, was negative, revealing clear spinal fluid which proved to be without organisms on smear, with but six cells, and sterile. The infection in the respiratory tract had largely subsided and the ears seemed uninvolved.

It was decided to treat this infant with the first of the sulfonamide drugs then available, prontosil, if his course, after the institution of other measures of treatment, suggested that he was not progressing as favorably as hoped for. As a result of this plan, observation was continued through Dec. 17, during which time the temperature gradually diminished, and the area of cellulitis on the leg showed signs of localizing. A new metastatic area of infection, however, had appeared on the right hand and the blood culture continued positive for the first two days, became negative Dec. 15, and positive again on Dec. 16 and 17. Late in the eve-

From the Departments of Pediatrics and Otolaryngology of the Washington University School of Medicine, and the St. Louis Children's Hospital.

TABLE I

INCIDENCE AND MORTALITY OF ACUTE PURULENT AND NONPURULENT MENINGITIS AND MENINGO-ENCEPHALITIS (DECEMBER, 1936, THROUGH MAY 15, 1942)

PURULENT	NO.	MORTALITY %	
		GROSS	CORRECTED*
Pneumococcal	24	75.0	63.7
Meningococcal	20	25.0	11.1
H. Influenzal	16	82.0	76.8
Hemo. strep.	12	33.3	11.1
B. Proteus	1	0.0	
Friedlander's	1	100.0	
Staph. + Strep.	1	100.0	
B. coli + Strep. viridans	1	100.0	
Sterile	24	0.0	
Total	100	41.0	29.4

NONPURULENT	NO.	MORTALITY %
Tuberculous	31	100.0
Syphilitic	6	16.7
Total	37	84.4

MENINGO-ENCEPHALITIS	NO.	MORTALITY %
Mumps	4	0
St. Louis	3	0
Measles	1	0
Undetermined	5	0
Total	13	0

*By excluding patients dying within the first twenty-four hours after admission to the hospital.

ning on Dec. 17 the temperature rose sharply again, and the next day definite meningeal signs and symptoms were noted. Spinal tap now revealed turbid fluid containing 4,500 cells, with streptococci seen on smear and later growing out on culture. With this turn of events it was decided to start chemotherapy and to combine with the intramuscular injection of prontosil continuous spinal drainage by the needle method and to provide continuous intravenous fluid administration. Such prompt improvement followed the institution of these measures that on the following day, Dec. 19, the spinal fluid culture was sterile, as were all later cultures. The blood cultures also became negative permanently, although it is to be noted from Chart 1 that the blood culture taken at the time of the development of meningitis was already sterile. In about forty-eight hours the temperature had become normal and continued to remain with no, or very little, elevation during a subsequent period of sulfanilamide administration. On Dec. 28 an abscess was drained which developed at the site of the original cellulitis. It was much like a cold abscess, but the pus contained viable hemolytic streptococci. The successful outcome of this case left a profound impression on all of us, since it was the first recovery in the St. Louis Children's Hospital of a patient with hemolytic streptococcal meningitis from whom the spinal fluid not only showed such organisms in stained smears, but also from which organisms could readily be grown on culture. It might be mentioned in passing that while the skin of this child became quite red during the period of prontosil administration, no discoloration of the spinal fluid with the red dye could be detected. No estimations were made of the concentrations of prontosil or sulfanilamide in the blood or spinal fluid since methods were not yet developed for such chemical determinations.

Follow-Up Examination.—When examined on April 4, 1942, some five years later, he was 6 years, 11 months old. It was learned that after returning home he had remained well and apparently was developing normally both physically and mentally. He weighed 45¼ pounds and was 45¼ inches tall. The physical examination revealed no abnormal findings. The appraisal of his mental status by one of us (B. S. K.) was as follows: When seen on the same date, the patient cooperated quietly but with some enjoyment, and sustained attention well, even in tasks which were of least interest to him. There was some shyness, but on the whole he answered questions readily.

The Stanford-Binet examination (Form L) yielded a mental age of 6 years, 6 months and an I.Q. of 94. There was a reasonable degree of uniformity, with best success in logical memory. Control of the pencil was rather poor in incidental drawings, in writing, and in the drawing of a man, which, nevertheless, earned (according to the Goodenough norms) a rating of 7 years, 3 months. Largely because of good sense of form relation, the patient earned a rating a year and a half above Binet mental age in a variety of performance tests drawn chiefly from the Pintner-Paterson scale.

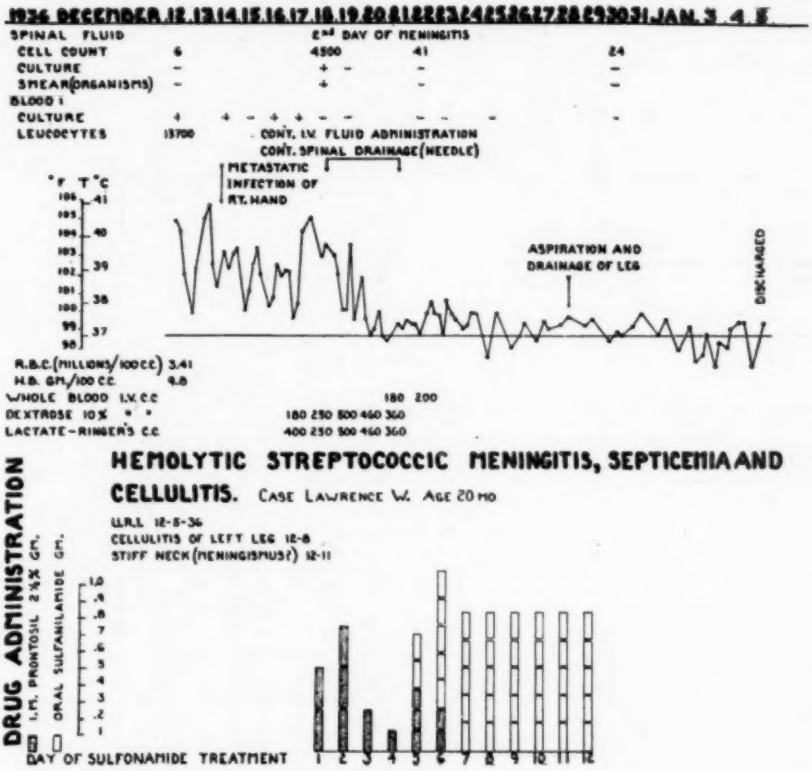

1926 DECEMBER 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 JAN. 3 4 5
SPINAL FLUID
2nd DAY OF MENINGITIS
CELL COUNT 6 4300 41 24
CULTURE – + – – –
SMEAR (ORGANISMS) – + – –
BLOOD
CULTURE + + – + + – – – – – –
LEUCOCYTES 13700
CONT. I.V. FLUID ADMINISTRATION
CONT. SPINAL DRAINAGE (NEEDLE)
METASTATIC INFECTION OF RT. HAND
°F °C
106 41
105
104 40
103
102 39
101
100 38
99
98 37
ASPIRATION AND DRAINAGE OF LEG
DISCHARGED
R.B.C. (MILLIONS/100 CC) 3.41
H.B. GM./100 CC. 9.8
WHOLE BLOOD I.V. C.C. 180 200
DEXTROSE 10% " " 180 250 500 460 360
LACTATE-RINGER'S C.C. 400 250 500 460 360
HEMOLYTIC STREPTOCOCCIC MENINGITIS, SEPTICEMIA AND CELLULITIS. CASE LAWRENCE W. AGE 20 MO
U.R.I. 12-8-36
CELLULITIS OF LEFT LEG 12-8
STIFF NECK (MENINGISMUS?) 12-11
DRUG ADMINISTRATION
I.M. PRONTOSIL 2½% GM.
ORAL SULFANILAMIDE GM.
1.0 .9 .8 .7 .6 .5 .4 .3 .2 .1
DAY OF SULFONAMIDE TREATMENT
1 2 3 4 5 6 7 8 9 10 11 12

Chart 1.

CASE 2 (Chart 2 and Table II).—This 3-year-old boy, W. B., developed acute bilateral purulent otitis media on Feb. 15, 1939. Approximately one month later, because of continued suppuration, bilateral simple mastoidectomy was performed. Extensive cellular destruction was noted, and hemolytic streptococcus was cultured from both mastoids. At this time the dura and lateral sinuses appeared normal. It should especially be noted that no preoperative chemotherapy was employed but that beginning on the second postoperative day 1.3 Gm. of sulfanilamide were administered daily from March 14 to 22. Both ears were then dry, the wounds were healing well, and the patient was discharged from the hospital. However, on May 5, 1939, meningeal symptoms developed without associated symptoms of acute respiratory infection. Admission to the hospital occurred on May 8, the

TABLE

DATE OF ADMISSION	CASE NO.	HISTORY NO.	RACE	SEX	AGE	BODY WT. (KG.)	APPARENT PORTAL OF ENTRY	APPARENT DAY OF MENINGITIS WHEN TREATMENT WAS STARTED	SULFONAMIDE		
									TOTAL		
									GM.	ADMINISTERED	GM. BEFORE FIRST NEGATIVE SPINAL FLUID CULTURE AND PERMANENT STERILIZATION
12/12/36	1	M-2302	W	M	1 yr. 8 mo	10.8	U.R.T.	Second	IM, 2.3 P O, 9.0 S	12 days	IM, 0.8 P
5/ 8/39	2	P-533	W	M	3 yr.	13.2	T.B. (?)	Fourth	O, 1.8 S O, 18.5 SP R, 21.6 SP	22 days	O, 8.5 SP
3/30/39	3	P-688	W	F	7 yr.	29.0	T.B.	Fifth	O, 69.0 SP IS, 0.4 S SC, 0.3 S	13 days	IS and SC, 3.1 S O, 6.0 SP
10/24/40	4	P-1648	W	M	3 yr.	15.7	U.R.T.	Fifth	O, 1.5 S O, 114.0 SP IS, 0.5 S IV, 32.4 S IV, 3.0 SP	45 days	IV, 4.5 SP
12/25/39	5	P-2635	W	F	2 mo.	4.5	?	First	O, 32.1 S IS, 1.3 S SC, 0.3 S IV, 0.8 SP	26 days	O, 2.4 S IS, 0.2 S IV, 0.8 SP
1/16/40	6	Q-169	W	M	5 yr.	14.5	T.B.	Third	O, 33.1 S O, 3.2 SP SC, 7.0 S IV, 2.3 SP	18 days	O, 3.0 SP IV, 1.5 SP
2/15/40	7	Q-328	W	M	7 yr.	15.0	T.B.	Third	O, 81.8 SMT O, 40.0 ST IV, 38.0 S IV, 0.8 SMT	36 days	O, 17.5 SMT IV, 15.0 S IV, 0.4 SMT
3/12/40	8	Q-500	W	M	6 yr.	16.6	T.B.	Fourth	O, 15.0 S O, 2.4 SMT O, 21.0 ST IV, 14.0 S IV, 2.6 SMT	14 days	O, 3.5 S O, 0.7 SMT IV, 2.5 S IV, 2.5 SMT Na
12/21/39	9	P-2617	W	M	6 mo.	5.6	T.B.	Fourth	O, 56.1 S O, 1.1 SP IS, 1.5 S IV, 0.3 S O, 5.5 SP	29 days	Never negative
6/ 2/38	10	O-1352	W	F	7 yr.	14.0	T.B. or sinuses	?	IS, 0.4 S SC, 2.8 S	6 hr.	–
1/29/39	11	P-271	W	F	8 yr.	Est. 20.0	T.B. or sinuses	Fourth	O, 0.6 S IS, 0.3 S SC, 2.5 S	12 hr.	–
2/12/42	12	S-391	W	M	1 mo.	3.7	T.B.	Second	IS, 0.2 S IV, 0.8 SC	3 hr.	–

*Organism found at autopsy.
U.R.T. = Upper respiratory tract.
T.B. = Temporal bone.
O = Orally.
IM = Intramuscularly.
IS = Intraspinously.
IV = Intravenously.
SC = Subcutaneously.
R = Rectally.
S = Sulfanilamide.

fourth day of meningitis. Purulent spinal fluid containing 6,400 cells was noted from which the hemolytic streptococcus grew on culture. The Tobey-Ayer test was negative at this time. Rapid improvement followed the oral and rectal administration of sulfapyridine. The temperature dropped to normal in less than forty-eight hours, and the spinal fluid became sterile on the third day. On the eleventh day of treatment, when the cell count was still a thousand or so, but after four successively negative spinal fluid cultures had been obtained, sulfapyridine administration was discontinued because the blood leucocyte count had

TABLE II

THERAPY		OTHER THERAPY			BACTERIOLOGIC DATA									
CONCENTRATION RANGE (MG. PER 100 C.C.)			MASTOIDECTOMY		BLOOD CULTURES				SPINAL FLUID				DAYS OF HOSPITAL STAY	OUTCOME
									SMEAR		CULTURE			
BLOOD	SPINAL FLUID	SPINAL DRAINAGE DAYS	SIDE	DAY OF TREATMENT WITH SULFONAMIDE	NO. TAKEN	NO. POS.	NO. NEG.	DAY OF TREATMENT WHEN LAST POSITIVE	FIRST	DAY OF TREATMENT WHEN LAST POSITIVE	FIRST	DAY OF TREATMENT WHEN LAST POSITIVE		
–	–	N, 3	–	–	9	4	5	First	C, +	First	+	First	21	R
2.4 to 10.7	1.1 to 6.4	–	–	–	7	0	7	–	I, +	Second	+	Second	13	R
4.9	–	–	L	Second	1	0	1	–	I, 0	–	+	Second	13	R
0 to 21	0 to 18.5	–	–	–	14	2	12	Second	I, +	Second	+	First	62	R
0 to 13.7	3.1 to 11.2	–	–	–	2	0	2	–	I, +	Fifteenth	+	Third	40	R
4.6 to 19.2	–	–	L	Fourteenth	2	0	2	–	I, +	First	+	First	28	R
4 to 10	0.8 to 7.6	N, 4	R	Seventh	7	1	6	–	C, +	Second	+	Sixth	126	R
2 to 20	1 to 13	N, 4	–	–	2	0	2	–	C, +	Second	+	Second	20	R
1.7 to 12.9	2.8 to 15	N, 4	–	–	9	0	9	–	I, +	Never negative	+	Never negative	29	D
–	–	–	–	–	1	0	1	–	I, –*	–	+*	–	6/24	D
–	–	–	–	–	1	0	1	–	I, +	–	+	–	13/24	D
–	–	–	–	–	1	1	0	–	C, +	–	+	–	2/24	D

SP = Sulfapyridine.
SMT = Sulfamethylthiazole.
ST = Sulfathiazole.
P = Prontosil.
Na = Sodium salt.
N = Needle method.
C = Correct.
I = Incorrect.
R = Recovered.
D = Died.

dropped to 3,400. It already had been reduced in amount for several days. On May 20, the thirteenth day, the temperature rose sharply, meningeal signs and symptoms recurred, and spinal tap again showed purulent fluid containing 7,100 leucocytes. At this time, however, organisms could not be seen on smear and a culture proved sterile. It should especially be noted that despite the previous leucopenia, with the recurrence of meningitis, the blood leucocyte count promptly rose to the very high level of 41,000. Sulfapyridine therapy was promptly resumed, and the temperature fell promptly to normal, and repeated spinal fluid

examination continued to show fluid free of organisms on stained smears and sterile, and on May 28 the cell count dropped to 136. A few days later, an irregular low-grade temperature was noted with a normal blood count and with substantially normal spinal fluid. No cause for this fever could be found, and it was presumed due to the drug, which was then discontinued. The prompt fall of the temperature to normal strongly suggested that the fever was due to drug administration.

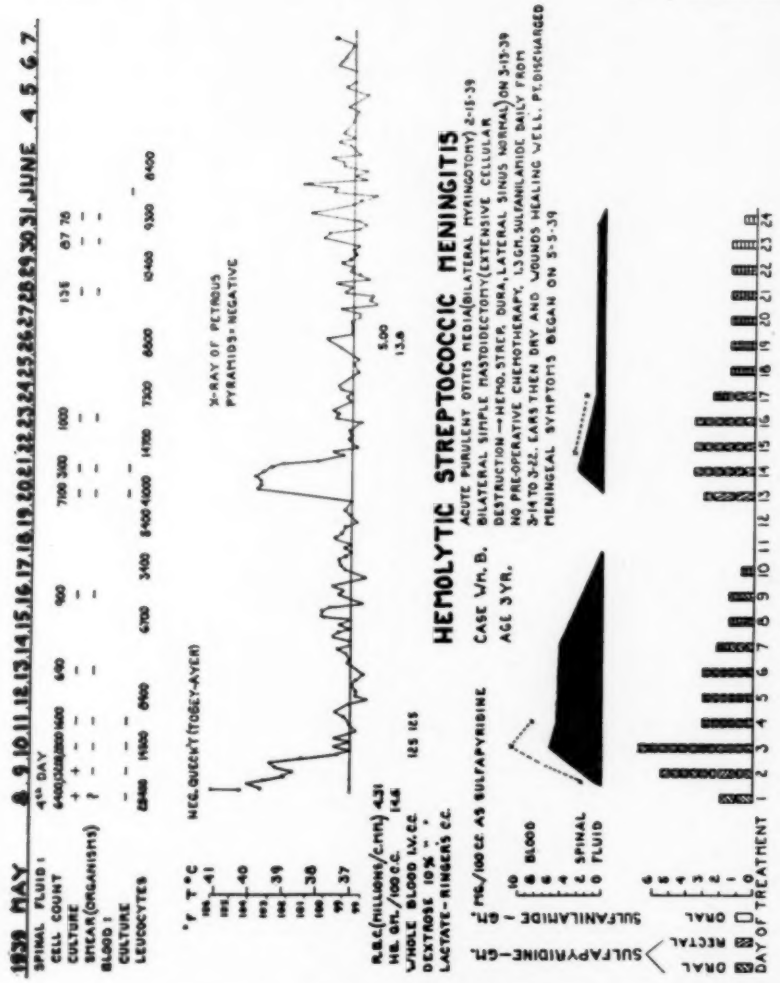


Chart 2.

The most instructive points about this case were the following: (1) Meningitis developed two months after bilateral mastoidectomy in the absence of symptoms or findings indicative either of lateral sinus phlebitis or of petrositis and in the absence of any acute respiratory infection; (2) recurrence of meningitis resulted apparently from the too early reduction and complete discontinuation of sulfona-

mide therapy which was prompted by the development of leucopenia; (3) the blood leucocyte count of 3,400 certainly could not be interpreted as due to dangerous bone marrow depression, since with the recurrence of meningitis just three days later the leucocyte count rose to 41,000; (4) the last bout of fever occurred when there were very low concentrations of sulfapyridine in the blood and spinal fluid and simultaneously with a change from sulfapyridine to sulfanilamide, which was going to be given until we were certain that the infection was thoroughly eradicated and disappeared promptly after complete cessation of drug administration. Another point of interest is that when pneumoencephalograms were made just one year later, on May 22, 1940, they were entirely normal and the interval history was in keeping with complete recovery from the meningitis without residual damage of any sort.

Follow-Up Examination.—This boy was again seen on Feb. 2, 1942, when he was 6 years, 2 months old, almost three years after recovery from the meningitis. Except for an attack of acute cervical adenitis a few months previously, he had been well since discharge from the hospital. He was in the first year of school and getting along well. His weight was 47 pounds, his height, 45½ inches. The physical examination was entirely negative. A mental appraisal made by one of us (B. S. K.) was as follows: The child was seen on Feb. 14, 1942. He cooperated with very serious interest, but was too shy to speak spontaneously and preferred to answer with a nod or a shake of the head whenever this was possible.

The mental age score in Stanford-Binet (Form M) was 6 years, 2 months, and the I.Q., 100. The range was narrow, and the lowest failures seemed very possibly due to shyness in speaking. Midscore in a selection of performance tests was above 10 years; cube imitation scored at the 12-year level, and only the manikin test scored below average. The drawing of a man earned a score of 9 years, 9 months.

It is probable that because of shyness the patient failed to do himself full justice where verbal responses were required. It was reported by the mother that school work in the first grade was satisfactory, except for writing.

Case 3 (Chart 3 and Table II).—J. M. S., 7 years of age, developed an upper respiratory tract infection on March 13, 1939. The left ear ruptured spontaneously on March 16, and ten days later meningeal symptoms were noted. On the fifth day of such symptoms, March 30, she was admitted to the hospital. The initial examination revealed the following: Purulent spinal fluid without organisms to be seen on smear but from which the hemolytic streptococcus grew on culture; a negative Tobey-Ayer test, purulent drainage from the left ear, which, on culture, grew out the hemolytic streptococcus; and x-ray evidence of mastoiditis on that side. The blood culture proved sterile. Treatment was started with a single initial subcutaneous dose of sulfanilamide, followed by an intraspinous injection and then was continued almost entirely by oral administration of sulfapyridine with two more injections of sulfanilamide intraspinously on the third and fourth days. From Chart 3 it may be noted that promptly following the institution of chemotherapy the temperature became much lower and the spinal fluid became sterile and remained so. Mastoidectomy was performed on the day after admission, and a coalescent type of mastoiditis with bone necrosis was noted. Cultures from the mastoid proved sterile. Neither the dura nor the lateral sinus was exposed during this operation. The temperature remained normal after the fifth day of treatment, which was continued altogether for thirteen days. Cyanosis from methemoglobinemia developed promptly after the institution of early and intensive sulfanilamide and sulfapyridine therapy. On the second day methylene blue

was given intravenously and later orally with good control of methemoglobinemia, which must have been due chiefly to the original dose of sulfanilamide, since subsequent administration of sulfapyridine was not associated with clinically significant degrees of methemoglobinemia.

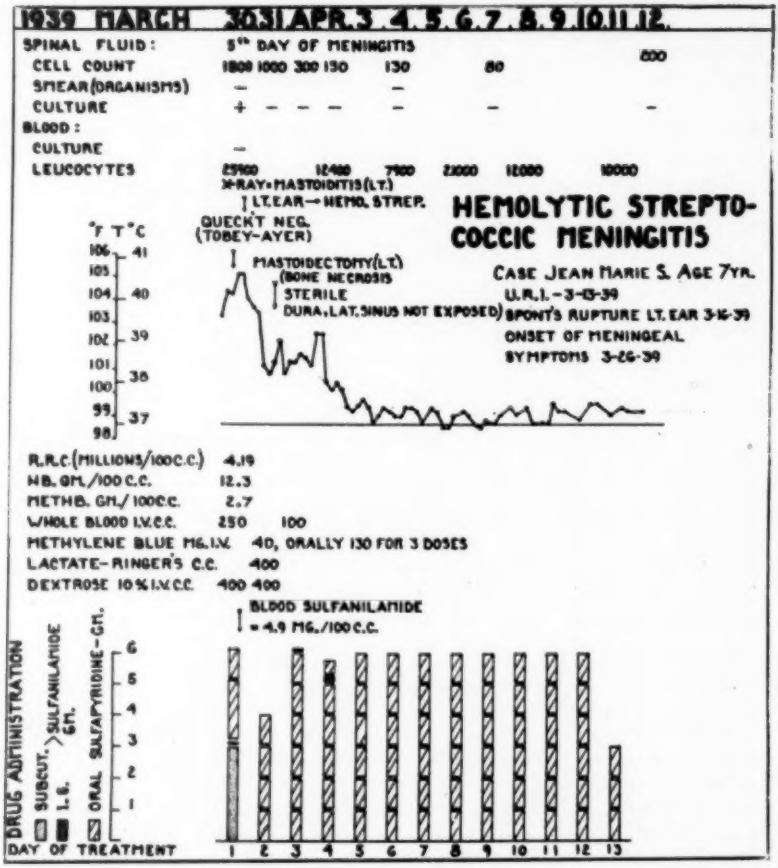

1939 MARCH 30 31 APR. 3 4 5 6 7 8 9 10 11 12
SPINAL FLUID:
5TH DAY OF MENINGITIS
CELL COUNT
1800 1000 300 130 130 80 600
SMEAR (ORGANISMS) – – –
CULTURE + – – – – – –
BLOOD:
CULTURE –
LEUCOCYTES 25900 12400 7900 22000 12000 10000
X-RAY: MASTOIDITIS (LT.)
LT. EAR — HEMO. STREP.
HEMOLYTIC STREPTOCOCCIC MENINGITIS
QUECKT NEG. (TOBEY-AYER)
MASTOIDECTOMY (LT.) (BONE NECROSIS STERILE DURA, LAT. SINUS NOT EXPOSED)
CASE JEAN MARIE S. AGE 7YR.
U.R.I. – 3-13-39
SPONT'S RUPTURE LT. EAR 3-16-39
ONSET OF MENINGEAL SYMPTOMS 3-26-39
°F °C
106 41
105
104 40
103
102 39
101
100 38
99
98 37
R.B.C. (MILLIONS/100 C.C.) 4.19
HB. GM./100 C.C. 12.3
METHB. GM./100 C.C. 2.7
WHOLE BLOOD I.V. C.C. 250 100
METHYLENE BLUE MG. I.V. 40, ORALLY 130 FOR 3 DOSES
LACTATE-RINGER'S C.C. 400
DEXTROSE 10% I.V. C.C. 400 400
BLOOD SULFANILAMIDE = 4.9 MG./100 C.C.
DRUG ADMINISTRATION
SUBCUT. SULFANILAMIDE GM.
I.V.
ORAL SULFAPYRIDINE - GM.
6 5 4 3 2 1
DAY OF TREATMENT 1 2 3 4 5 6 7 8 9 10 11 12 13

Chart 3.

Follow-Up Examination.—This girl was seen again on Feb. 7, 1942, when 10 years, 5 months old, and some three years after recovery from the attack of meningitis. Her parents stated that she had returned to school shortly after her discharge from the hospital and that her teacher expressed herself as feeling that the girl behaved just as she had before her illness. During the winter following discharge from the hospital, there was again purulent drainage from both ears. Subsequently she remained healthy. Physical examination was negative. Mental appraisal by one of us (B. S. K.) was as follows: This girl was seen Feb. 9, 1942; at that time she was in the fifth grade. She cooperated willingly and seemed fully self-confident.

The Stanford-Binet examination (Form L) showed a mental age of 13 years, 8 months, and an I.Q. of 131. There was some scatter, with lowest failures in similarities, in interpreting a picture, and in constructive visual imagination, and best work in reversed digits, in the code test, and in arithmetic reasoning. Performance work scored at the same level as the Binet. Manual dexterity was no more than average, and cube imitation scored at 15 years. The Goodenough, scoring at 13 years, 3 months, was a normal adolescent drawing, well proportioned and well executed.

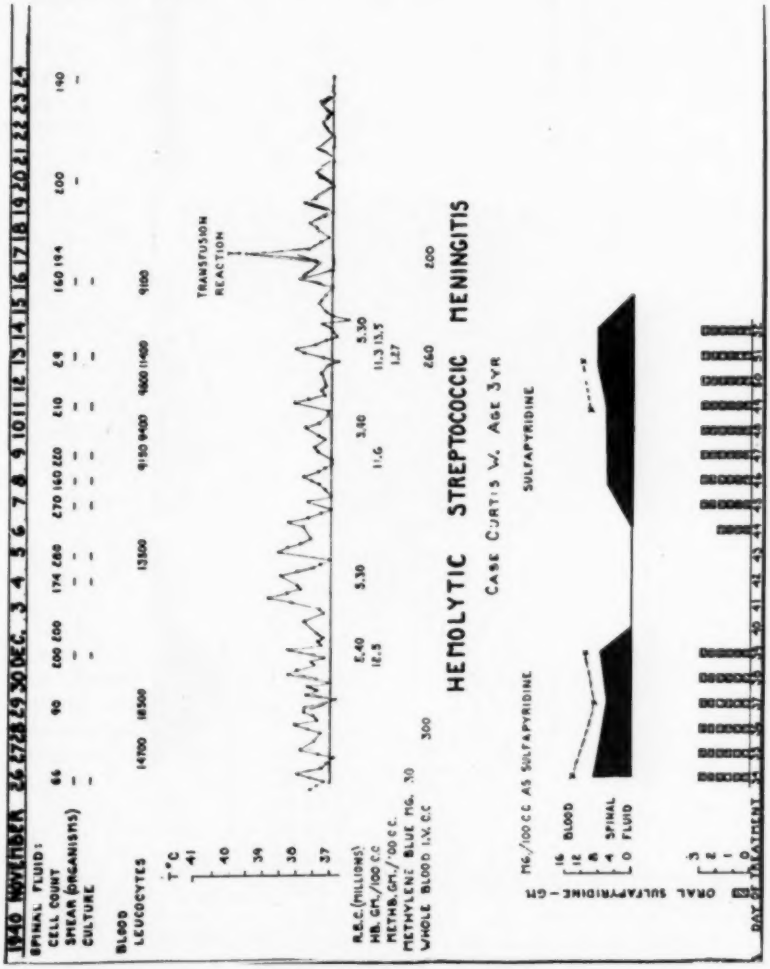


Chart 4A.

CASE 4 (Charts 4*A* and 4*B* and Table II).—C. W. was a 3-year-old boy when admitted. Apparently he had had his first respiratory infection, a rhinitis, at 1 year of age, and his adenoids had been removed at 2 years of age because of repeated colds. On Oct. 16, 1940, he again developed an acute upper respiratory tract infection and became very ill. Meningeal symptoms appeared on Oct. 20.

Admission to the hospital occurred on Oct. 24, the fifth day of meningitis. The initial examination revealed an extremely ill boy whose spinal fluid was purulent, the smear showing many gram-positive diplococci in short chains. It could not be certain from this smear whether these organisms were streptococci or pneumococci. The Tobey-Ayer test at this time was negative. In addition to the meningitis,

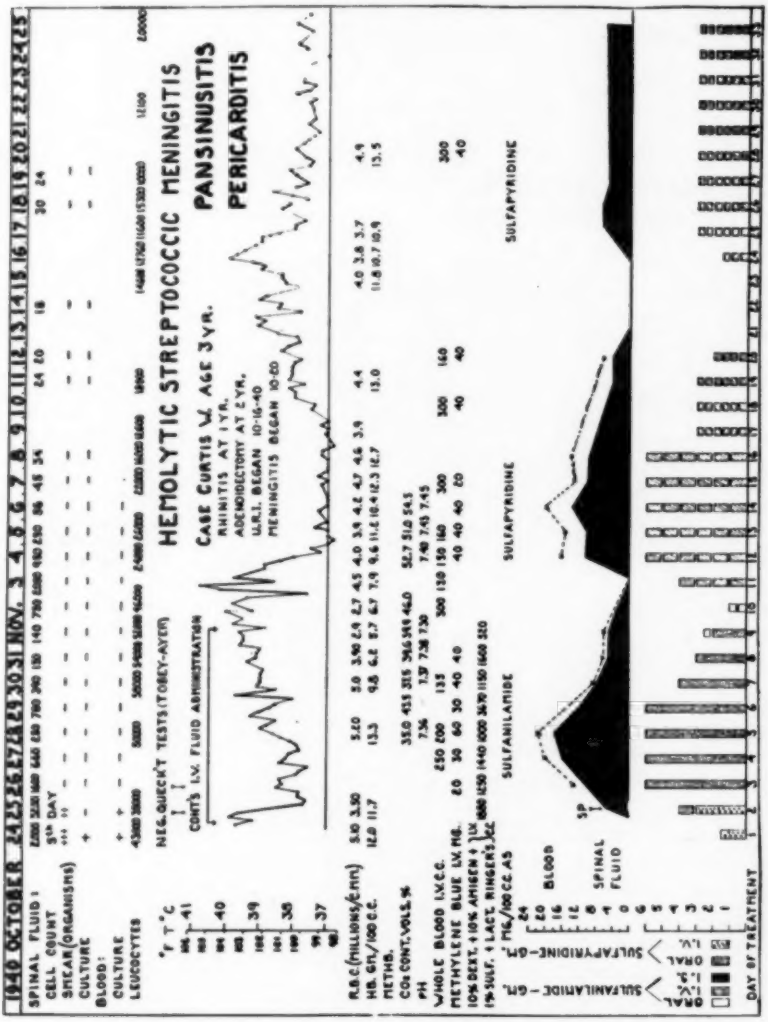
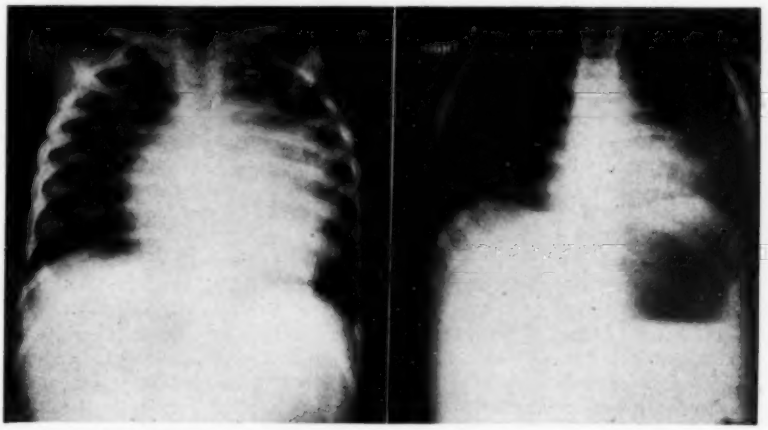


Chart 4B.

there was a severe generalized upper respiratory tract infection with tonsillitis and sinusitis. The ears, however, were almost normal in appearance. There was also pericarditis with pericardial effusion (Fig. 1). Cultures from throat, blood, and spinal fluid on admission grew out hemolytic streptococci. The pericardial fluid, however, proved sterile, even though purulent.

Treatment was begun with the intravenous administration of sodium sulfapyridine which was changed to sulfanilamide the following day when the cultures revealed the presence of hemolytic streptococci. At this stage in our experience we felt as others did at the time, that perhaps sulfanilamide was without question the drug of choice for hemolytic streptococcal infections, an idea which now is no longer tenable. It is to be noted that promptly after the administration of sodium sulfapyridine the temperature dropped critically, almost to normal, and although the spinal fluid cell count increased, the number of organisms on smear diminished and even on the second tap the culture already was sterile and continued to remain so. The blood culture remained positive until the third day. After substitution of sulfanilamide for sulfapyridine therapy, the spinal fluid cell count continued to diminish until a low count of 140 was noted on Nov. 1, the ninth day of treatment. Throughout this period of sulfanilamide therapy, however, the temperature continued gradually to mount, and the blood leucocyte counts remained at a very high level. The sulfanilamide was administered by the continuous intravenous injection method along with dextrose and lactate-Ringer's solution.



A. *B.*

Fig. 1.—Cardiac silhouettes of patient in Case 4. *A* was made Oct. 30, 1940; *B*, Nov. 15, 1940.

On the fourth and fifth days of treatment blood drug concentrations of approximately 20 mg. per 100 c.c. were obtained with almost as high spinal fluid concentrations. Because of the rising temperature with falling cell count in the spinal fluid, which continued to remain sterile, drug fever was thought possible, and the dosage of sulfanilamide was gradually reduced until on the eleventh day of treatment the blood concentration fell almost to zero. On this day, Nov. 3, the temperature rose sharply, meningeal signs and symptoms again appeared, and a spinal tap revealed purulent fluid with two thousand cells. Organisms, however, could not be seen on smear nor could they be cultured. Sulfapyridine therapy was then resumed, the drug being given orally this time with very prompt control of the fever and with rapid clearing of the spinal fluid. The dosage of the drug was cut in half when the temperature had been normal for approximately five days and when the spinal fluid cell count had reached 34. Shortly afterwards the temperature again mounted with, however, a continued low cell count of the spinal fluid. Drug fever was again thought possible, and sulfapyridine administration was discontinued completely. There followed still higher fever, so sulfapyridine therapy

was again resumed. The temperature then fell promptly to a lower level but did not reach normal. On the fortieth day drug administration was again discontinued and again a higher temperature promptly followed, which again returned to a lower level with resumption of sulfapyridine administration on the forty-fourth day. The drug was discontinued for good on the fifty-third day, after which the temperature remained normal or very slightly elevated with the exception of one single spike on Dec. 17, the result of a transfusion reaction. By Nov. 15 the pericardial effusion had completely disappeared, and a normal cardiac silhouette was noted (Fig. 1). At no time were the ears definitely involved, and mastoiditis seemed not to be considered as a probable portal of entry for the meningitis in this case. Simultaneously with the recovery from meningitis and pericarditis, tonsillitis and sinusitis also subsided. On Nov. 11 all the sinuses seemed clear in the conventional x-ray film, but laminagrams showed cloudiness still of the right posterior ethmoid cells. We felt that the continued low-grade fever, which would so strikingly increase when sulfapyridine therapy was discontinued and disappear with resumption of such treatment, was due either to this residual ethmoiditis or to some residual pocketed meningitis with good walling off but causing still a continued slight increase in cells in the spinal fluid.

Follow-Up Examination.—This boy was seen on Jan. 31, 1942, a little more than a year after recovery from the meningitis, and when he was 4 years, 4 months old. According to his father, there were no signs or symptoms related to the central nervous system during the interval. He was, however, subject to "colds" and had had one attack of sore throat with fever. He weighed 39½ pounds and was 42¾ inches tall. On physical examination, large, chronically infected tonsils were found. There was still the strabismus due to the weakness of the left sixth intracranial nerve, which the parents had stated was present before the involvement of the meninges.

Mental appraisal by one of us (B. S. K.) was as follows: He came into the room somewhat unwillingly as he was tired from a long wait. He was overactive, and at times playfully negative; attention span was relatively short.

The Stanford-Binet examination showed a mental age of 3 years, 11 months and an I.Q. of 90. The patient did best at tasks that could be grasped and carried out at once, but was less successful where prolonged effort was needed. Performance work was average. There was no lack of uniformity in the examination which could not be traced to restlessness and varying attention.

Case 5 (Chart 5 and Table II).—This girl, V. B., was but 6 weeks of age when admitted to the hospital on Dec. 25, 1939. Fever and irritability had been present for twelve hours and convulsions for four hours prior to admission. Initial examination revealed absolutely nothing other than meningeal signs and symptoms. The spinal fluid was purulent, and organisms were seen on smear for the first three days, during which time they also grew on culture. Chemotherapy was begun with an intravenous injection of sodium sulfapyridine, followed by intraspinal and then oral administration of sulfanilamide. Combined sulfapyridine and sulfanilamide treatment was continued on the second and third days. As in all previous cases, prompt initial fall in temperature was noted. During this period the spinal fluid first increased in cell count and then showed a prompt diminution in the number of cells. A return of fever was noted which remained low grade from the fourth to the thirteenth day, when sulfanilamide only was being administered, and when spinal fluid concentrations of the drug averaged less than 8 mg. per 100 c.c. During this time, although the spinal fluid remained sterile and without organisms to be seen on smear, an abnormally high cell count, averaging more than 300 per cubic millimeter, was constantly noted. On the thirteenth day the concentration of sulfanilamide in the spinal fluid dropped to less than 4 mg. per 100 c.c. The temperature rose sharply, meningeal signs reappeared, the spinal

fluid again became turbid and for the next four days continued to show organisms on smear although they would not grow on culture. The dose of sulfanilamide was then doubled from the fourteenth through the twenty-first day of treatment; and the temperature again was slowly brought under control and the spinal fluid grad-

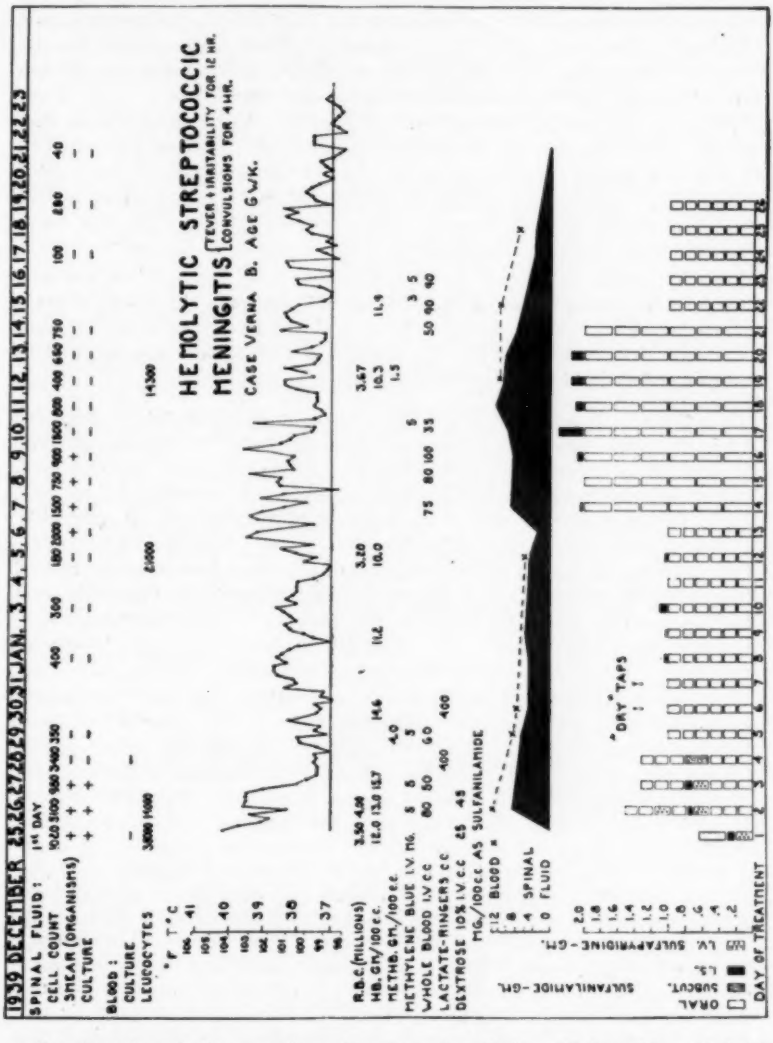


Chart 5.

ually cleared, and the organisms disappeared entirely. During this period the spinal fluid sulfanilamide concentrations averaged about 10 mg. per 100 c.c. Fever persisted from the twenty-second to the twenty-sixth day of treatment despite clear spinal fluid with relatively few cells. Because of this, drug fever was suspected and the drug discontinued. The temperature then promptly fell to normal and remained so. During the hospital stay, the measurements of head circumfer-

ence remained normal. No pneumoencephalograms, however, were made. As mentioned previously, nothing at all was noted which would suggest a portal of entry for the meningitis. As in previous instances when sulfanilamide and sulfapyridine were used, considerable cyanosis due to methemoglobinemia developed and was controlled by the administration of methylene blue from time to time. Also, as in previous cases, anemia was never permitted to develop to any dangerous degree, normal red counts and hemoglobin values being maintained by suitable transfusions. In this patient, as in the patients in Cases 2 and 4, it was very difficult to determine just when it was safe to discontinue chemotherapy.

Follow-Up Examination.—This girl was seen again on March 10, 1942, more than two years after recovery from the meningitis which had developed when she was only 6 weeks old. The parents stated that she had had some difficulty in sleeping for a while after returning home and then seemed perfectly normal and bright and with good muscular coordination. Physical examination was negative except for enamel defect usually described as "hereditary opalescent dentine."

Mental appraisal by one of us (B. S. K.) was as follows: Patient was seen when she was 2 years, 4 months old. Because of her extreme shyness which made it difficult to elicit spoken responses, the I.Q. of 100 (Stanford-Binet, Form M) was considered to be minimal. That the rating was at least average suggested that no impairment of intellectual function was present.

CASE 6 (Chart 6 and Table II).—J. H., a 5-year-old boy, complained of pain in his left ear eight days before admission to the hospital. The ear ruptured two days later, and two days before admission he developed headache and stiff neck. He received his first sulfonamide drug on the second day of meningeal symptoms, 1.5 Gm. sulfapyridine by mouth. When admitted on the third day of meningitis, on Jan. 16, 1940, the initial examination revealed the following: Cloudy spinal fluid containing, however, only 750 cells; gram-positive cocci were seen on stained smear and when grown proved to be hemolytic streptococci; the blood culture at this time proved to be sterile; the Tobey-Ayer test was at first questionably positive on the left but later proved frankly negative on four separate occasions; x-ray examination revealed changes characteristic of mastoiditis on the left.

Treatment was begun with orally administered sulfapyridine and intravenously administered sodium sulfapyridine, and, after approximately twenty-four hours, sulfanilamide was also given subcutaneously. After the third day only sulfanilamide was administered, orally and subcutaneously. As in all of the previous cases, a prompt temperature fall was noted almost immediately after institution of sulfonamide chemotherapy with, however, a later recurrence of fever. Also, as in other instances, when the initial cell count of the spinal fluid was low and organisms numerous, the earliest change was a decrease in the number of organisms with increase in the number of leucocytes. As early as on the second day organisms no longer could be seen, and the spinal fluid proved sterile although the leucocyte count of the spinal fluid had risen from 750 to 5,000. On the ninth day of the treatment, after the amount of sulfanilamide administered had been somewhat reduced and the spinal fluid concentrations, which had averaged close to 9 mg. per 100 c.c., had fallen to approximately half that level, a sharp rise in temperature was noted with an increase in the cell count of the spinal fluid from a low of 27 on Jan. 21, the sixth day of treatment, to 760 on Jan. 24. The dosage of sulfanilamide was then increased to its previous level of 0.3 Gm. per kilogram per day, again with prompt fall in temperature and cell count of the spinal fluid. It is to be noted that after the first day the spinal fluid continued to remain sterile and without visible organisms on smear. On the fourteenth day of sulfonamide treatment a left simple mastoidectomy was performed. Mastoid cells were found

lined with a gray pyogenic membrane but were not broken down. Both dura and lateral sinus were quite normal. Following this operation the temperature gradually returned to normal. On Feb. 8 an x-ray of the petrous pyramid was interpreted as showing petrositis on the left. The boy was discharged on Feb. 13, apparently completely recovered from the meningitis.

As in some of the previous cases, frequent transfusions had to be given to counteract the tendency toward anemia, probably the result both of infection and drug administration. Considerable methylene blue had to be given first intravenously and later orally to control methemoglobinemia, and at the start of treatment considerable parenteral fluid was required and administration of the drug was largely parenteral during the first few days.

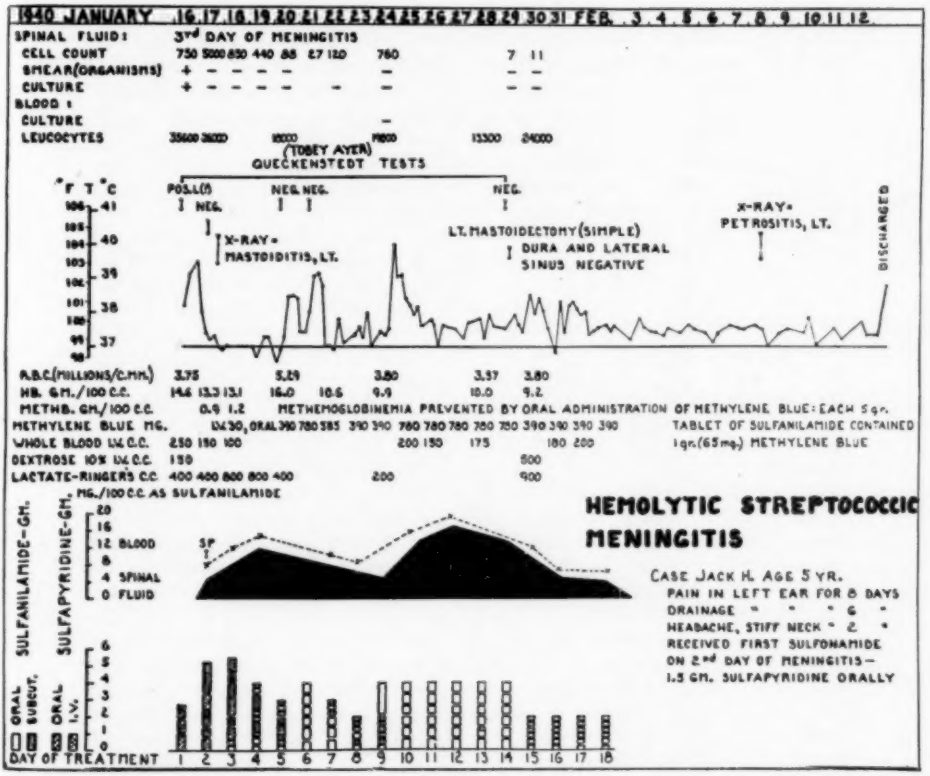

1940 JANUARY 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 FEB. 3 4 5 6 7 8 9 10 11 12
SPINAL FLUID: 3rd DAY OF MENINGITIS
CELL COUNT 750 5000 850 440 88 27 120 760 7 11
SMEAR (ORGANISMS) + - - - - - - - - -
CULTURE + - - - - - - - - -
BLOOD:
CULTURE -
LEUCOCYTES 35600 36000 15000 7800 13300 24000
(TOBEY AYER) QUECKENSTEDT TESTS
POS. L(5) NEG. NEG. NEG. NEG.
°F °C
X-RAY - MASTOIDITIS, LT.
LT. MASTOIDECTOMY (SIMPLE)
DURA AND LATERAL SINUS NEGATIVE
X-RAY - PETROSITIS, LT.
DISCHARGED
A.B.C. (MILLIONS/C.MM.) 3.75 5.29 3.80 3.37 3.80
HB. GM./100 C.C. 14.6 13.3 13.1 16.0 10.6 9.9 10.0 9.2
METHB. GM./100 C.C. 0.9 1.2
METHEMOGLOBINEMIA PREVENTED BY ORAL ADMINISTRATION OF METHYLENE BLUE: EACH 5 gr. TABLET OF SULFANILAMIDE CONTAINED 1 gr. (65 mg.) METHYLENE BLUE
METHYLENE BLUE MG. 0.4 30, ORAL 390 780 585 390 390 780 780 780 780 780 390 390 390 390
WHOLE BLOOD C.C. 250 150 100 200 150 175 180 200
DEXTROSE 10% C.C. 150 500
LACTATE-RINGER'S C.C. 400 400 800 800 400 200 900
MG./100 C.C. AS SULFANILAMIDE
SULFANILAMIDE-GM. SULFAPYRIDINE-GM.
BLOOD SPINAL FLUID
SP
HEMOLYTIC STREPTOCOCCIC MENINGITIS
CASE JACK H. AGE 5 YR.
PAIN IN LEFT EAR FOR 6 DAYS
DRAINAGE " " " 6 "
HEADACHE, STIFF NECK " 2 "
RECEIVED FIRST SULFONAMIDE ON 2nd DAY OF MENINGITIS — 1.5 GM. SULFAPYRIDINE ORALLY
ORAL SUBCUT. ORAL I.V.
DAY OF TREATMENT 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Chart 6.

Follow-Up Examination.—This boy was again seen on Jan. 31, 1942, two years after recovery from the meningitis. His parents stated that he had been quite well since returning home, but that he seemed a little "nervous" and fidgety the first year. He weighed 40¾ pounds, and was 46¼ inches tall. During the physical examination, which was otherwise entirely negative, he seemed apprehensive and blinked his eyes frequently.

Mental appraisal by one of us (B. S. K.) was as follows: When seen on the same date, the patient was 7 years, 1 month old and in the second grade. He co-

operated willingly but was not at ease and batted his eyes a good deal. He worked cautiously, but answered readily and expressed himself well.

The Stanford-Binet examination (Form L) yielded a mental age of 6 years, 10 months. Performance work scored at the same level, but the Goodenough drawing rated nearly a year higher. While no serious interference with effort was manifest, the fact that the patient was doing acceptable work in the second grade suggested the possibility that he had failed to do himself full justice in this examination.

CASE 7 (Chart 7 and Table II).—This 7-year-old boy, J. M., developed a generalized acute upper respiratory infection on Feb. 11, 1940, which included bilateral otitis media. Just two days later meningeal symptoms began and admission to the hospital occurred on the third day of meningitis, Feb. 15, 1940. The initial examination revealed a very seriously and acutely ill boy with spinal fluid literally teeming with streptococci, proved later on culture to be hemolytic. Cell count of this initial tap was only 380. The Tobey-Ayer test was already positive on the right side, and the blood culture proved also to be positive on the day of admission. Treatment was started with a single dose of sodium sulfamethylthiazole followed by sulfamethylthiazole given orally. From the second through the fourteenth day of sulfonamide treatment, both sulfamethylthiazole and sulfanilamide were administered, the total dosage averaging about 0.4 Gm. per kilogram of body weight per day. The temperature fell steadily after the beginning of treatment, and the boy showed gradual improvement. While organisms could not be seen in the spinal fluid on the second day and thereafter, they continued to grow on culture for the first six days, after which the spinal fluid continued to be sterile. As in previous cases of a similar nature, immediately after treatment the spinal fluid cell count rose as the number of organisms diminished, and then fell. On the seventh day of sulfonamide treatment, after the blood culture had been sterile for five days, and on the first day of sterile spinal fluid, ligation of the right internal jugular vein was made, and then a right simple mastoidectomy was performed with exposure and incision of the lateral sinus. Mastoid cells everywhere were found involved; granulations spread over the knee of the lateral sinus, and, where exposed, the dura was found red and thickened. The temperature then slowly returned toward normal. The spinal fluid continued to show some increase in cell count but remained without organisms to be seen, and always sterile, findings possibly to be explained by some remaining pocket of infection. Strabismus and dilated pupils were the only neurologic findings suggestive of continued central nervous system involvement.

As in the previous cases, there was need for considerable supportive treatment, especially early in the course of the infection, and for about thirteen days fluid was given by the continuous intravenous injection method, consisting of dextrose and lactate-Ringer's solution to which sulfanilamide was added for the total sulfanilamide administration during this period. For the first four days continuous spinal fluid drainage was also effected. The spinal fluid concentrations averaged about 7 mg. per 100 c.c. during the period when organisms continued to be grown on culture. Also, as in the patients in some of the previous cases, a transient leucopenia was noted, the blood count dropping from 23,500 on Feb. 16 to 6,400 on Feb. 19. The dosage of the drug, however, was not reduced, and on Feb. 21 the count doubled. On April 6 the tonsils and adenoids were removed, and on April 17 he was transferred to Ridge Farm, our country convalescent department, to complete his recovery. He was finally discharged from the hospital on June 19, 1940, completely recovered except for a dilated and fixed right pupil.

Follow-Up Examination.—This boy was again examined on Jan. 31, 1942, approximately two years after recovery from the meningitis. His parents stated

that he had been quite normal since returning home. His weight was 50¼ pounds, and his height, 50¾ inches. The right pupil was dilated and fixed, but no other physical abnormalities were noted.

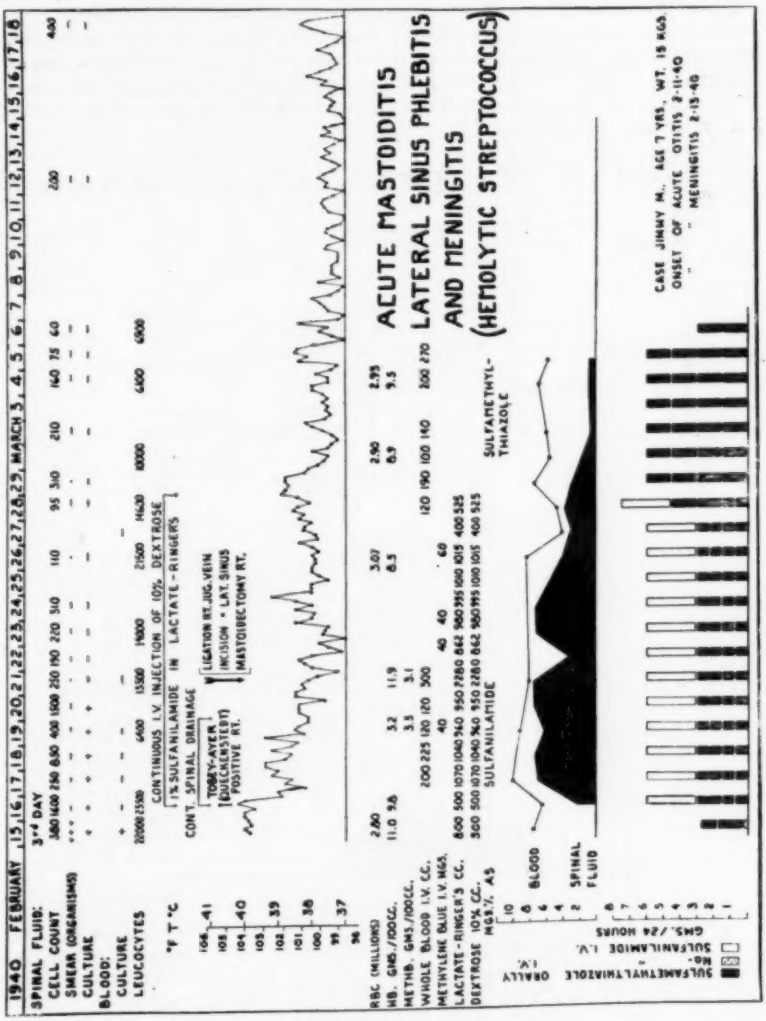


Chart 7.

Mental appraisal by one of us (B. S. K.) was as follows: When seen on Feb. 11, 1942, the patient was 9 years, 10 months old and in the last quarter of the second grade. Effort and attention were fair, and he got some pleasure from the tasks, but to some extent restlessness interfered with attention. Patient was unable to say the sound of *sh*, and had to substitute the sound of *s*.

The Stanford-Binet examination (Form L) yielded a mental age of 7 years, 2 months, and an I.Q. of 73, with a range of four years. When asked for

similarities, patient seemed able to give only color differences; he failed in detecting pictured absurdities and in comprehension. Best work was in constructive visual imagination and in making change. Performance work was variable; the formboard work was generally high average, but the manikin scored at 5 years, and the cube imitation and Healy Picture Completion I at the Binet level.

The patient is reported to be getting along well in a grade about two years below expected placement. The lack of uniformity in scores in different types of ability may be greater than would be accounted for by restlessness and superficial attention, and it is possible that the ratings are not representative of original intellectual endowment.

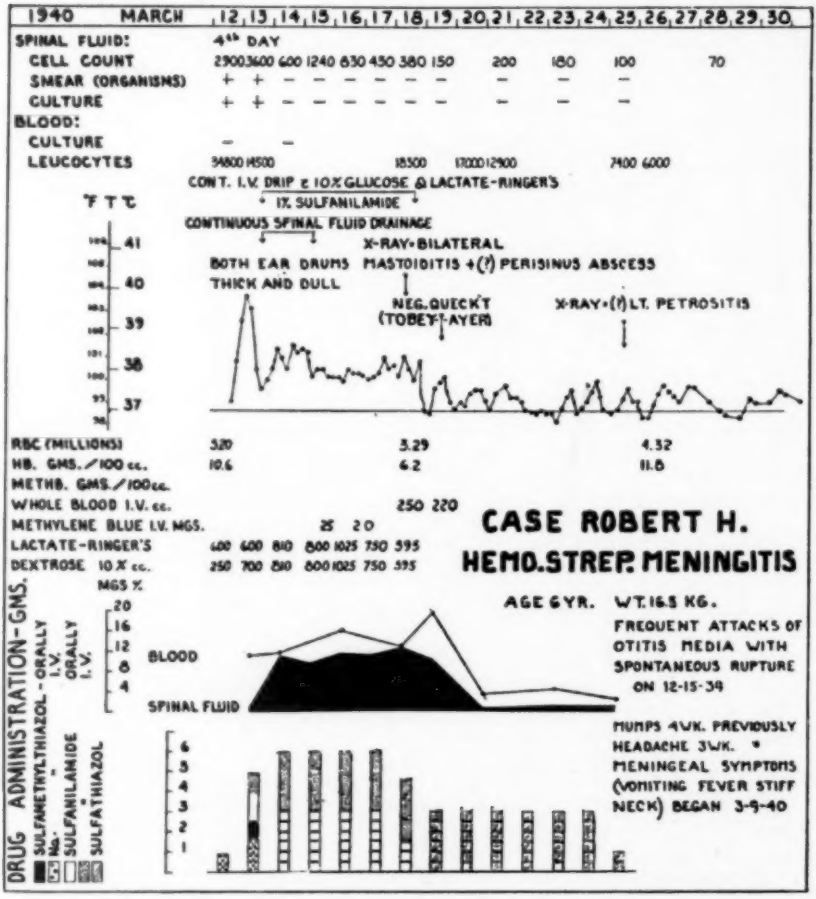


Chart 8.

CASE 8 (Chart 8 and Table II).—This 6-year-old boy, R.H., had the history of frequent attacks of otitis media with spontaneous rupture of the drums on Dec. 15, 1939. Some four weeks prior to admission, on March 12, 1940, he developed mumps, complained of headaches a week later, and developed clear-cut meningeal

symptoms with vomiting, high fever, and stiff neck on March 9. On admission he was in his fourth day of meningitis, thought at first possibly to be due to mumps. The initial examination, however, revealed purulent spinal fluid with organisms seen and grown as hemolytic streptococci. Treatment was started as sodium sulfamethylthiazole intravenously, followed by sulfamethylthiazole orally and sulfanilamide orally and intravenously. Spinal fluid smears and cultures persisted positive on the second day, but thereafter were negative. Spinal fluid cell counts first rose and then diminished rapidly. The temperature fell sharply initially, and then continued to decline at a less rapid rate. On admission both eardrums were intact but somewhat thick and dull, and a little later x-ray examination was interpreted as revealing bilateral mastoiditis with a questionable perisinus abscess on the left side. The Tobey-Ayer test, however, was frankly negative. Later another x-ray examination was interpreted as revealing questionable petrositis on the left side. Early in the course of the infection continued spinal fluid drainage by the needle method was employed, and fluid was given by a continued intravenous injection method, which included administration of sulfanilamide. Also, a number of transfusions were given, and on two occasions methylene blue had to be given to control methemoglobinemia. Spinal fluid concentrations of sulfonamide averaged about 10 to 12 mg. per 100 c.c. while both drugs were administered and then fell sharply to very low levels when only sulfathiazole was given. By this time, however, the infection seemed well under control. Because of the minimal involvement of the ears, it was the opinion of members of the department of otolaryngology, and we agreed, that mastoidectomy was not necessary unless further trouble developed which could be attributed to middle ear and mastoid infection.

REPORT OF FATAL CASES

CASE 9 (Chart 9 and Table II).—This boy, C. C., 6 months old when admitted, developed an acute upper respiratory infection about one month prior to admission with drainage from one ear, exactly which side was not remembered. About one month later, on Dec. 17, 1939, signs of acute upper respiratory infection were again noted, and the next day, Dec. 18, meningeal symptoms developed. He was admitted to the hospital on Dec. 21, the fourth day of meningitis. The initial examination revealed purulent spinal fluid containing a great many organisms seen on smear and on culture, proving to be the hemolytic streptococci. Throughout the whole course of this disease the spinal fluid continued to be grossly purulent, finally becoming so thick that an accurate cell count could not be made; it continued also to teem with viable organisms. After approximately twenty-four hours of treatment with sulfapyridine alone, given both intravenously as the sodium salt and orally, treatment was continued as sulfapyridine administered intravenously and sulfanilamide orally and intraspinously. Despite an early promising temperature fall to normal with a subnormal temperature persisting for approximately four days, no other signs of improvement were noted, and after the fifth day of treatment fever was continuous until shortly before death on Jan. 17, 1940. During the first fifteen days of treatment, spinal fluid concentrations never exceeded 8 mg. per 100 c.c. Later, with increased drug dosage, somewhat higher levels were obtained but never higher than 15 mg. per 100 c.c.

At autopsy extensive brain involvement was noted as described in the following pathologic report by Dr. W. O. Russell, of the Department of Pathology: The dura was adherent to the underlying leptomeninges in several places, and when it was sectioned, a large amount of purulent fluid containing fibrin was revealed. Both cerebral hemispheres were of softer consistency than normal, and there was purulent material in the ventricles. The meningitis was quite marked also at the base of the brain, but here the nervous tissue was of normal con-

sistency. There was thick exudate over the whole of the brain surface. Grossly, the air cells of both mastoids were observed to contain purulent exudate, and there was exudate in the middle ears.

Post-mortem otorhinologic report by D. Wolff: Severe bilateral chronic purulent otitis media, mastoiditis, and labyrinthitis were present (Figs. 2 and 3).

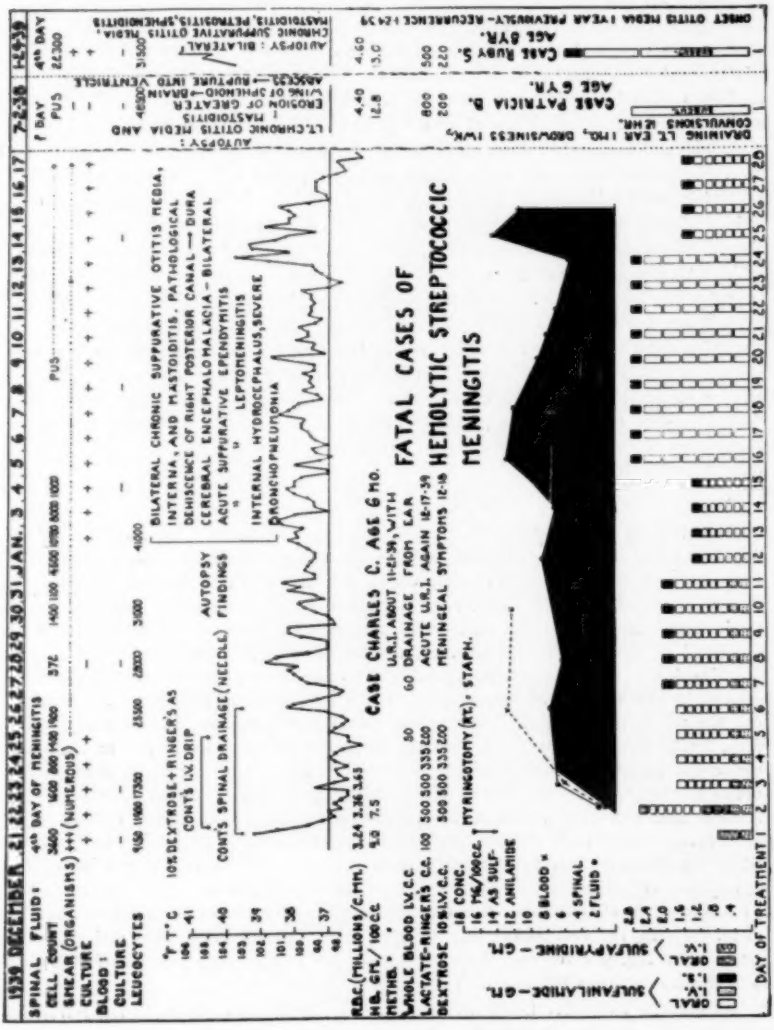

FATAL CASES OF
HEMOLYTIC STREPTOCOCCIC
MENINGITIS
CASE CHARLES C. AGE 6 MO.
CASE PATRICIA B. AGE 6 YR.
CASE RUBY S. AGE 6 YR.
ONSET OTITIS MEDIA 1 YEAR PREVIOUSLY- RECURRENCE 1-24-39
DRAINING L.E. EAR 1 MO., DROWSINESS 1 WK.,
CONVULSIONS 12 HR.
DAY OF TREATMENT
SULFANILAMIDE — GM.
SULFAPYRIDINE — GM.
ORAL
I.V.
I.M.
SPINAL
BLOOD
FLUID
AUTOPSY:
LT. CHRONIC OTITIS MEDIA AND MASTOIDITIS
EROSION OF CRANIUM
SINUS OF SPHENOID → BRAIN ABSCESS → RUPTURE INTO VENTRICLE
CHRONIC SUPPURATIVE OTITIS MEDIA, MASTOIDITIS, PETROSITIS, SPHENOIDITIS
BILATERAL CHRONIC SUPPURATIVE OTITIS MEDIA, INTERNA, AND MASTOIDITIS. PATHOLOGICAL DEHISCENCE OF RIGHT POSTERIOR CANAL — DURA
CEREBRAL ENCEPHALOMALACIA — BILATERAL
" ACUTE SUPPURATIVE EPENDYMITIS
" LEPTOMENINGITIS
INTERNAL HYDROCEPHALUS, SEVERE
BRONCHOPNEUMONIA
10% DEXTROSE + RINGER'S AS CONT'S I.V. DRIP
CONT'S SPINAL DRAINAGE (NEEDLE)
AUTOPSY FINDINGS
U.R.I. ABOUT 11-29-38, WITH DRAINAGE FROM EAR
ACUTE U.R.I. AGAIN 12-17-38
MENINGEAL SYMPTOMS 12-18
RYANIGOTOMY (RT.) - STAPH.

Chart 9.

Direct extension of pus into both labyrinths occurred through the footplates of the stapes (Fig. 6), through the round window membranes (Fig. 4), and by erosion of the bony walls into both horizontal canals, as illustrated for the left in Fig. 7. There was erosion of the posterior canal leading from the pus-filled labyrinth on

the right to the dura (Fig. 5). The ductus endolymphaticus on each side was laden with pus. Marrow in the petrous apex was hyperactive and the cells distorted in shape. A minute pathologic dehiscence was also seen from the nose, extending intracranialward near the cribriform plate (Fig. 8).

Fig. 2 (Case 9—8495).—Horizontal section of right ear, showing pus in mastoid antrum, middle ear, labyrinth, and internal auditory meatus. The arrow in the vestibule points to the oval window through which direct extension from the middle ear occurred. See high power (Fig. 6).

Fig. 3 (Case 9—8495).—Horizontal section of left ear. The mastoid antrum and aditus on this side exhibit a more chronic state as evidenced by the web of fibrous tissue binding submucosa of the antrum with malleo-incudal joint.

CASE 10 (Chart 9 and Table II).—This 6-year-old girl, P. B., was admitted on July 2, 1938, in a moribund condition, dying approximately four hours after admission and after but a single dose of sulfanilamide could be administered subcutaneously. There was a history of a draining left ear for one month, drowsiness

for one week, and convulsions for twelve hours prior to admission. A spinal tap made immediately after admission revealed extremely cloudy fluid with too many leucocytes to be counted accurately and with much fibrin. The blood leucocyte count was extremely high, being 48,500. At autopsy it was found that a brain abscess had ruptured into the ventricle, and this abscess had apparently developed

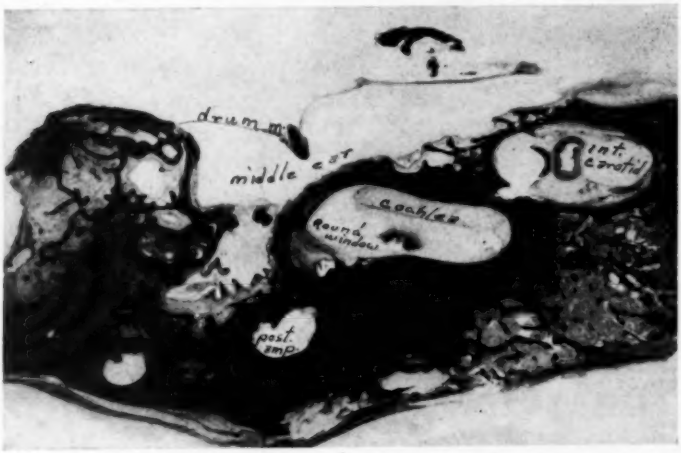


Fig. 4 (Case 9—8495).—Horizontal section of left ear at the level of round window which is completely eroded and offers a route of direct extension from middle ear to labyrinth.

Fig. 5 (Case 9—8495).—Horizontal section of the left ear, showing the unclosed bony facial canal at the level of the oval window and the marked pathologic erosion of the nonampullated limb of the horizontal canal as it returns to the vestibule. Note fistula from posterior canal to dura.

as a result of erosion of the greater wing of the sphenoid. There was also found a chronic left otitis media and mastoiditis. A report of the general pathologic findings by Dr. J. H. Wedig, Department of Pathology, is as follows: A filmy exudate was present about the base of the brain. The posterior tip of the greater

wing of the left sphenoid bone showed an erosion about 1 cm. in diameter. The brain over this area showed a round soft demarcated area which on cut section revealed a left cerebral abscess moderately encapsulated and extending into the ventricle. Abscess and ventricle contained purulent exudate.

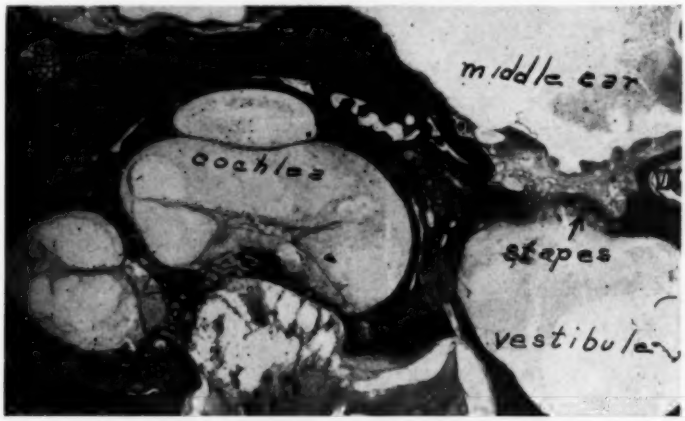


Fig. 6 (Case 9—8495).—Detail of Fig. 2, showing a mere fragment of footplate of stapes remaining in the oval window.

Fig. 7 (Case 9—8495).—Detail of Fig. 5, showing the unclosed facial canal (a normal state for this 6-month-old infant) and the marked pathologic erosion of the bony wall of the horizontal canal.

Post-mortem otologic report by D. Wolff: Gross examination of the petrosae at autopsy revealed the presence of unusually large superior petrosal sinuses on each side, and each of these took a more exposed and lateral course than usual before entering the cavernous sinus. There was free flow of blood from the sinuses. On the left a dark spot was seen on the surface of the dura over the left mastoid portion of the temporal bone, posterior to the arcuate eminence. Microscopic examination revealed a heavily infected mastoid, middle ear (Fig. 10), and eustachian tube. The drum membrane was not remarkably thickened, but both mucosal

and epidermal layers were sloughed off in areas. Prussak's pouch was laden with pus. Direct extension of infection from a pus-filled angle cell in the mastoid through pathologic dehiscences of bone could be traced into both the middle cranial and the posterior cranial fossae (Fig. 9). The dehiscence through the

Fig. 8 (Case 9—8495).—Pathologic dehiscences from the nasal cavity through the cribriform plate intracranialward.

Fig. 9 (Case 10—7516).—Vertical section through left mastoid, showing direct extension superiorly into the middle fossa and postero-inferiorly into the posterior fossa.

tegmen antri into the middle fossa was 2 mm. in length and from 2 to 5 mm. in width. Over this lay heavily infected dura. The internal carotid artery in this petrosa contained a blue staining exudate, and clumped in the upper border were

what appeared to be badly distorted red blood cells. This condition suggested a vascular block in some portion of this artery. Marrow cells in the apex of the petrosa appeared shrunken and crenated. The end organs of the inner ear showed

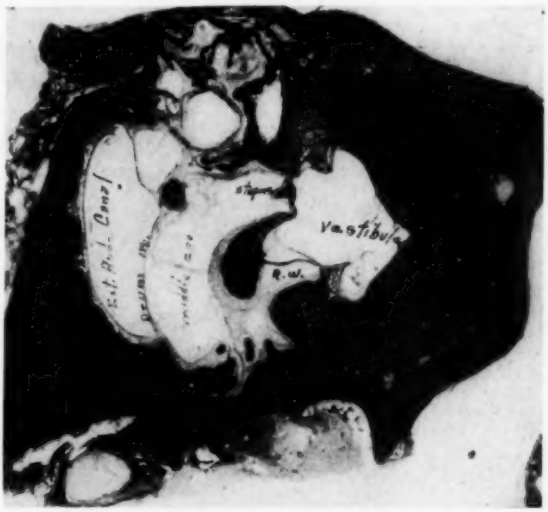


Fig. 10 (Case 10—7516).—Vertical section through the middle ear and vestibule. Note the thickened mucosa over the promontory and the strands of cicatricial tissue extending across the middle ear.

Fig. 11 (Case 11—7921).—Horizontal section of the right ear, showing long fimbria projecting into the eustachian tube.

atrophic degeneration. A few free blood cells were seen in the scala tympani. The right ear was essentially normal at the time of death but with evidence of a past infection.

In summary, there seem to have been two avenues of entry of infection to the meninges in this case. There was a route from the nasopharynx eroding through the sphenoid bone, causing a brain abscess which had ruptured into the ventricle, and there was also a route of direct extension from the infected left mastoid and middle ear.

Fig. 12 (Case 11—7921).—Horizontal section of the left ear, showing mastoid, aditus, and retrolabyrinthine cells filled with pus. Anteriorly a pathologic dehiscence into the internal carotid canal is seen.

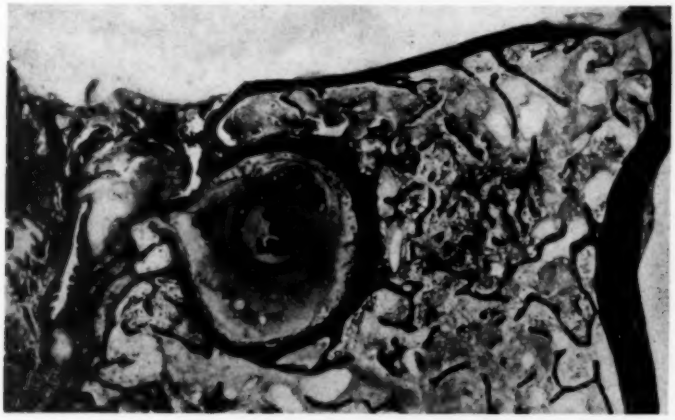


Fig. 13 (31).—Not belonging to this series of cases but illustrating pericarotid venous sinus thrombosis and involvement of the pericarotid sheath in *Strep. hemolyticus* infection in a 4-year-old boy. Specimen received prior to the days of chemotherapy.

CASE 11 (Chart 9 and Table II).—This girl of 8 years, R. S., was also admitted in a moribund condition, dying thirteen hours after admission. There was a history of otitis media one year prior to admission with a recurrence on Jan. 24, 1939. She was admitted to the hospital on Jan. 29, 1939, apparently on the fourth

day of meningitis. The spinal fluid was very cloudy, containing 22,300 cells; organisms could be seen on smear and grown on culture. Two doses of sulfanilamide were given subcutaneously and one intraspinously before death occurred. The general findings at autopsy were reported by Dr. F. Woolsey, Department of Pathology, as follows: In addition to generalized leptomeningitis more marked in the right temporoparietal and basilar regions, there existed bilateral chronic suppurative otitis media, mastoiditis, and sphenoiditis.

Post-mortem otorhinologic report by D. Wolff: Bilateral chronic otitis media petrositis and mastoiditis were present (Figs. 11 and 12), that on the right being more active at the time of death. Both mastoids showed empyemic membrane partially filling many of the pneumatic spaces, in the center of which were pockets of pus. Numerous long fimbria, which were infiltrated with cells, protruded into the lumen of the eustachian tubes (Fig. 11). Multiple minute pathologic dehiscences of the bony wall of the carotid canal were seen on the left. On the right a minute dehiscence was observed leading into the posterior fossa.

In this instance the contents of the carotid canal were not secured at autopsy. Consequently, we cannot state whether the single dehiscence seen on the right was the origin of the meningitis or whether the carotid sheath on the left played a role. Such an origin for meningitis has been well established, and Fig. 13 demonstrates an abscess arising from pericarotid venous phlebitis in a 4-year-old child.

CASE 12 (Table I).—This 5-week-old boy, J. J., was said to have had a draining ear for a week previous to entry to the hospital. Treatment may have included some sulfonamide drug. Eighteen hours prior to admission he had a generalized convulsion and became suddenly much more acutely ill with marked pallor, difficult respiration, and rapidly increasing stupor.

On admission on Feb. 12, 1942, the initial examination revealed a markedly dehydrated infant, semistuporous and showing Cheyne-Stokes respiration, with marked slowing of the heart rate during the apneic periods. The heart sounds were very poor and the general picture was that of circulatory collapse. The left ear appeared normal, but the right ear showed purulent drainage. The fontanel was soft and the spine flexible, but the deep reflexes were absent and there was a positive Brudzinski's sign, inequality of the pupils and strabismus. The temperature was only 37° C. Lumbar puncture revealed grossly purulent spinal fluid loaded with streptococci which on culture proved to be hemolytic. The Tobey-Ayer test was negative. Blood culture and culture from the right ear were also positive for hemolytic streptococci. Fifteen cubic centimeters of 1 per cent sulfanilamide solution were injected into the spinal canal during the lumbar puncture, and intravenous chemotherapy was begun with sodium sulfadiazine, 2 c.c. per kilogram of a 5 per cent solution. Parenteral fluid was given with the infant in an oxygen tent. No improvement occurred, and the child expired about two and one-half hours after entry. No sulfanilamide was found in the spinal fluid drawn prior to drug administration in the hospital.

Post-mortem examination by Dr. W. Kenney revealed a generalized purulent leptomeningitis, an acute inflammatory process in the left mastoid antrum, and bronchopneumonia of the right lower lobe. Temporal bone studies have not as yet been completed.

DISCUSSION

Etiology.—In the twelve cases of hemolytic streptococcal meningitis just described, this condition seemed definitely to have been related to acute or neglected infection in the upper respiratory tract in all but two patients, Cases 2 and 5. In Case 2 such a relationship probably

also existed, in that this boy had apparently satisfactorily recovered from otitis media and mastoiditis without the aid of adequate chemotherapy but with bilateral mastoidectomy, only to develop meningitis some two months later without obvious cause. It seems to us that it is more than possible that the meningitis developed as a result of residual infection in the temporal bone (petrous pyramid?), which surgical intervention failed to reach and drain and which remained dormant possibly because of chemotherapy too much delayed, of inadequate dosage, and of too short duration. We feel justified in this assumption because chemotherapy later apparently proved adequate in effecting a permanent cure without further surgery. Some hesitancy should also be felt in considering Case 5 an exception. This child was but 6 weeks of age, and it is easily possible for temporal bone infection to have existed without eardrum changes of significance. Such cases have been observed by one of us (D. W.). Of the ten cases with upper respiratory tract relationship, nine definitely had otitis media and three had mastoiditis confirmed by operation (Cases 3, 6, and 7), and four more had temporal bone infection proved by autopsy, which in three instances at least seems to have been the probable cause of the fatal meningitis (Cases 9, 10, and 11). In another instance, Case 8, mastoid involvement was indicated by x-ray. This child recovered without mastoidectomy.

The close relationship in infants and children of hemolytic streptococcal infections, temporal bone pathology, and fatal meningitis is well established by the temporal bone studies from a variety of sources by one of us (D. W.), a brief résumé of which follows:

Temporal bones have been studied from twenty-six cases of otitis media in which the *Streptococcus hemolyticus* was recovered from some region of the body. The identification of this organism was made before death in seventeen cases. It was recovered from the ear in seven of the seventeen patients. The aural diagnosis was reinforced by finding the organism also in the blood in two of these patients, in the spinal fluid in one, and in an aspirated brain abscess in another. In a fourth case streptococcus not identified as hemolyticus was found in the spinal fluid. In this case streptococcus was also found in the blood. In a fifth case streptococcus not identified as hemolyticus was found in the blood, reinforcing the finding of *Strep. hemolyticus* in the ear. In the remaining twelve patients the organism was recovered either from the blood or spinal fluid or both, or from a localized abscess. In the nine remaining cases it was found only at the post-mortem examination.

The twenty-six patients include only three adults. Seven of the patients were under 1 year of age. It was evident from the histories that all individuals old enough to explain their difficulty, and not moribund, had at some time complained of severe earache. Mastoid tenderness on the other hand was not a characteristic symptom, having been elicited only eight times as compared with fifteen complaints of earache. There is evidently a distinct tendency for spontaneous rupture

of the drum membrane to occur in these patients, as it was found in fifteen instances. Myringotomy was performed in sixteen cases, two of these being in the opposite ear from that in which the spontaneous rupture occurred.

On the whole, these cases terminated very swiftly, only two having long-standing otitis media, one of these for one and one-half years, the other having had chronic sinusitis for seven years. Three cases had had their symptoms less than five days, and eleven others had been sick just three weeks or less. Fourteen of the children appeared well developed and well nourished at autopsy.

Vomiting occurred in fifteen cases. One of these was in an infant with pyloric stenosis, and one in an infant with bacillary dysentery. In six cases vomiting occurred only once or twice. In the nine remaining cases it occurred several times. In this group was a twenty-four-year-old pregnant woman who also had purulent labyrinthitis, and a twelve-year old (described as having continuous vomiting) who had purulent labyrinthitis, as shown in the microscopic sections. Nystagmus was not a common observation, being found definitely in only four cases. A fifth case was described as turning the eyes upward. Mastoid operations were done on ten of these cases, three of these being bilateral operations. Two radical operations were done. One simple operation was repeated. Septicemia, as proved by blood culture, was present in nine cases. Sinus thrombosis was present in eight cases. Meningitis occurred in seventeen cases, brain abscess in five, the remaining patients dying chiefly from pneumonia and one of endocarditis. Post-mortem kidney changes were recorded in nine patients, bacterial emboli being found once. Cloudy swelling was reported in the others.

A study of the microscopic sections of the temporal bones revealed bilateral otitis media in six cases in which only one ear had been treated clinically. Direct extension by pathologic erosion of bone could be demonstrated in eighteen cases. Evidently this disease is characterized by rapid dissolution of delicate bone trabeculae. It apparently attacks bone even more readily than connective tissue, for purulent labyrinthitis with extension through the round or oval window occurred in only four cases. Most cases showed a clear inner ear, sometimes with relatively normal organs of Corti. Vascular routes could be demonstrated in two, and in a third both the vascular and direct routes of extension were noted. Apicitis occurred in twelve cases. In four of these the infection was within the bony carotid canal.

Diagnosis.—Since the seriousness of the condition makes the immediate diagnosis and treatment of meningitis urgent, prompt measures to establish the diagnosis and institute therapy should always be taken when there is any suggestion that the meninges might be infected. In the presence of history, physical findings, of x-ray evidence of otitis media and mastoiditis, or of serious upper respiratory tract infection, it is well to be on the alert for meningeal signs and symptoms. When-

ever physical findings indicative of meningeal irritation are present, immediate lumbar puncture with examination of the spinal fluid is indicated. Main reliance for the diagnosis of meningitis must always be placed on this test. It has been argued that performance of lumbar puncture in the presence of serious infection elsewhere in the body and especially in the presence of bacteremia is a dangerous procedure. The point should be emphasized, however, that wide clinical experience has proved that danger of contamination of uninfected meninges by lumbar puncture seems much more theoretical than real,[2] and the advantage to be gained from the avoidance of loss of time in starting treatment by far outweighs any such danger. Advantage should be taken at the time of such a diagnostic puncture of performing also the Tobey-Ayer modification of the Queckenstedt test, especially if there exists otitis media and the picture of sepsis with, therefore, the possibility of lateral sinus phlebitis and thrombosis.

The fluid once obtained should be examined by stained smears and by culture. In the examination of the smears certain pitfalls must be avoided. As may be seen from consulting Table II, in eight of the cases incorrect conclusions as to the identity of the infecting organism were drawn from examination of the original smears, and the first impressions later proved to be incorrect by the culture results. The use of the Gram stain technique is often misleading if one is not thoroughly familiar with the method and the appearance of organisms when so stained. Decolorization to too great a degree on the one hand and failure to decolorize sufficiently on the other may lead to a wrong decision as to the nature of the organism; for example, meingococci may be mistaken for pneumococci or vice versa. Decisions based on stained smears, therefore, should be made only by those skilled in interpreting their significance. Culture results will usually correct any errors thus made but may take twenty-four to forty-eight hours in returning.

The finding of purulent spinal fluid with or without organisms visible on smear must be taken as an indication for the immediate institution of proper therapy. In this connection, it may be noted that in Case 10 no organisms were seen on smear and that growth was obtained only from the autopsy culture. We have included in another group to be discussed in a later paper those cases in which confirmation of the nature of the organisms was not obtained by culture, although in some of them organisms were visible on the stained smear. This group of so-called "sterile" meningitides show some striking differences from those in which there were positive cultures. It may also be seen from examination of Table II that in one case in which organisms were not visible in the stained smear they nevertheless grew out in culture. From these facts the conclusion may be drawn that it is always important to obtain cultural confirmation of the diagnosis of type of meningitis, but that institution of chemotherapy because of the broadness of coverage of the newer drugs should not wait upon accurate cultural data. Serum

therapy, however, we believe should not be used without accurate bacteriologic diagnosis because of its specificity, greater risk of danger of administration, and its much greater expense.

Treatment and Results.—If the mortality of the twelve cases presented be corrected by the exclusion of the three cases which were moribund on admission, the resulting mortality is one of nine, or 11 per cent, which compares favorably with results of sulfonamide therapy of hemolytic streptococcal meningitis already reported in the literature.[3] This is in striking contrast to the results obtained at the St. Louis Children's Hospital before the advent of chemotherapy, there being not a single recovery among those cases in which organisms were actually obtained on culture from the spinal fluid.

If we turn our attention first to the recovered cases, we are immediately impressed by the speed with which infection in the meninges was brought under control by all three of the drugs used (Table II). In three instances (Cases 1, 4, and 6) positive spinal fluid cultures were obtained on only the first day, in three more (Cases 2, 7, and 8) on only the first two days, in Case 5 for the first three days, and in Case 7 for the first six days. What seems also important is the fact that in not one instance was there a return to positive cultures after the first negative had been secured. This is in marked contrast to what so frequently is noted in influenzal, and to a somewhat less degree, in pneumococcal meningitis, where relapse, which includes a return to positive cultures, is quite common.

Complete eradication of the infection does *not* occur so quickly, however, if we are to judge from the frequent tendency toward persistence of fever, increased cell count* in the spinal fluid, blood leucocytosis, and the occasional recurrence of acute meningeal signs and symptoms (Cases 2, 4, 5, and 6) with return to purulent, though sterile, fluid. Because of such a tendency, and because of the apparently greater difficulty in eradicating infection completely from the temporal bone, continuation of drug administration, sometimes for long periods, seems unavoidable.

The question of when to discontinue chemotherapy is one of the most difficult to answer, and, it seems to us, must always be decided for each individual case.

If a coalescent type of mastoiditis exists and can be diagnosed with certainty, surgical intervention will be necessary for complete eradication of the infection in the mastoid process of the temporal bone. There is no advantage of delaying such an operation beyond the time required for control of the infection in the meninges, and it would seem wiser to perform such an operation when the subject is still receiving full doses of the drug. Unnecessary operative delay and long continuation of sulfonamide therapy on the other hand might lead to the development

*Later increase in the cell count is not to be confused with the favorable and almost invariable rise which occurs on the second day of treatment and is associated with diminution of the number of organisms.

of serious toxic manifestations from drug administration, which in turn may make necessary discontinuation of chemotherapy and operative intervention without its protection. Subsequent spreading of the infection may thereby result. If, on the other hand, the nature and the extent of the involvement of the temporal bone are doubtful, and either bone destruction is thought not present or infection is thought to be in some inaccessible part of the bone, as, for instance, the bony carotid canal, long-continued chemotherapy would seem indicated. In some instances it may be difficult to diagnose accurately conditions within the temporal bone by any method short of operative inspection. Exploratory mastoidectomy we feel is often justified and may be safely performed *after* meningitis is under control and while the patient is still receiving full doses of sulfonamide drug. Such a procedure should not, however, be undertaken too early in the course of infection or before the drug and the patient have been given ample opportunity to overcome the infection completely.

Such principles as those stated above were followed in most of our successfully treated cases. In Cases 1, 4, and 5, no evidence of temporal bone involvement existed, and there was no surgical intervention seriously contemplated. In Case 8 the subsidence of infection in the middle ears and the improvement of the drum membranes during treatment of the meningitis, together with the x-ray finding of just cloudiness of the mastoid region on both sides without clean-cut evidence of cell breakdown, prompted us to refrain from surgical exploration. In Case 2 bilateral simple mastoidectomy had already been performed and occurrence of meningitis was without associated localizing evidence of infection in the temporal bone. There was, therefore, no choice but to rely entirely on chemotherapy. In Case 7 six days of chemotherapy were allowed to elapse during which time the meningitis was brought under control and the septicemia abolished before operative intervention was thought safe. In reviewing Case 6, we are inclined to believe that decrease in drug dosage was made too soon and surgical exploration postponed too long, permitting exacerbation of meningeal signs and symptoms, which required a second period of intensive chemotherapy. It should be noted that when mastoidectomy was performed on the fourteenth day of treatment, no breaking down of cells was present which was in keeping with the x-ray finding of simple cloudiness of the mastoid. It is unfortunate that a culture was not made of the bone, the cells of which were found lined with pyogenic membrane, to determine whether or not viable organisms were still present. In Case 3, surgical intervention was performed perhaps earlier than desirable with, however, only some rise in fever as a postoperative reaction.

If we turn next to the fatal cases, we note that in two of them (Cases 10 and 11), despite long-standing infection in the temporal and sphenoid bones, no chemotherapy had been employed until they were admitted to the hospital in moribund condition. Much the same could be said of

the other case (Case 9). In this instance, we question seriously, in light of our more recent experiences with intensive chemotherapy, whether sufficient drug was ever administered, since spinal fluid concentrations never exceeded 15 mg. per 100 c.c. and for the first two weeks were well under 10 mg. per 100 c.c. Such levels were probably too low for the heaviness of the infection, the spinal fluid at all times teeming with organisms.

It is from this experience and other experiences such as this (especially in pneumococcal and *Hemophilus influenzae* infections) that we have come to feel that while low concentrations of sulfonamide drugs may suffice to sterilize the spinal fluid in some instances, in others quite high concentrations are needed. It seems best to start with large enough doses to cover the latter cases and to reduce the amount of drug administered if the larger doses are later found unnecessary. In our earliest cases the dosage rarely exceeded 0.3 Gm. per kilogram body weight per day; now our initial dosage for the first few days averages 0.6 Gm. per kilogram per day. Sulfadiazine seems to be the best drug at present, with sulfapyridine second choice. The poor diffusion of sulfathiazole into the spinal fluid, regardless of the explanation,[4] must be given due consideration and prompts us to give sulfathiazole an inferior ranking for the treatment of most acute pediatric infections. We have witnessed the development of pneumococcal meningitis (to be reported in a later paper) during sulfathiazole treatment of otitis media, the meningitis responding later quite promptly to sulfadiazine. Instances of pneumococcal meningitis following immediately upon the successful treatment of pneumonia with sulfathiazole have also been reported.[5]

Sulfanilamide, despite its lower order of effectiveness and its greater tendency to produce objectionable central nervous system symptoms, methemoglobinemia, and anemia, possesses some advantage. When parenteral administration is necessary and intravenous administration of sodium salts difficult, it can quite safely and easily be administered subcutaneously or intraperitoneally. It is also compatible with all solutions likely to be given intravenously, such as dextrose, lactate-Ringer's and amigen solutions, whole blood or plasma; and, finally, when dissolved in "artificial" spinal fluid,[6] may be given intrathecally without irritation and with the desirable effect of producing very high, if but temporary, spinal fluid concentrations.

The value of spinal drainage is considerably in doubt. Laminectomy we have always felt undesirable because of the subsequent difficulty of securing specimens of spinal fluid fit for bacteriologic examination. Invariably, staphylococci gain entrance, and confuse the picture. Ureteral catheter drainage seems open to the same objection. Continuous needle drainage, which was employed in four of our cases, may occasionally be of some value, particularly in late cases with very thick spinal fluid, and requiring much supportive parenteral fluid therapy.

Not only can the danger of too greatly increased spinal fluid pressure in such cases be easily avoided, but bacteriologic sampling of the spinal fluid is also made easy and with little danger of contamination.

While we agree with Hoyne[7] that frequent lumbar punctures are usually unnecessary for treatment, information so gained lends much to the understanding of the clinical picture and may sometimes be the only reliable means of determining whether to increase drug dosage in the presence of continued fever or to discontinue such administration entirely. Subsequent studies may also prove that such frequent punctures are of assistance in controlling internal hydrocephalus, which, we are now beginning to believe, frequently develops and may persist for some time after infection has disappeared.

SUMMARY AND CONCLUSIONS

Careful study has been made of twelve patients with hemolytic streptococcal meningitis admitted to the St. Louis Children's Hospital since treatment with sulfonamide drugs has been possible. It may be concluded that this infection almost invariably is a complication of acute or neglected infection in the upper respiratory tract and usually in the temporal bone. In three fatal cases of this series, and in twenty-six others, the involvement of the meninges was shown usually to have been the result of direct extension of the infection from the middle or inner ear, the mastoid or petrous portion of the temporal bone, or from the pericarotid veins in the carotid sheath. Complete recovery with little or no residua in eight of the twelve patients is to be attributed to both early and accurate diagnosis, adequate administration of sulfonamide chemotherapy, adequate supportive treatment of all types, and to surgical drainage of accessible suppuration within the temporal bone.

We wish to express our appreciation of the valuable service rendered by Dr. M. M. Cook in photographing the illustrations which are reproduced in this paper.

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STUDIES WITH HEMOPHILUS PERTUSSIS

X. Comparative Antigenic Analysis of Bacillus Parapertussis and Hemophilus Pertussis, Phase I, With Consideration of Clinical Significance

Earl W. Flosdorf, Ph.D., A. Bondi, Ph.D., Harriet Felton, M.D., and Aims C. McGuinness, M.D., Philadelphia, Pa.

HPERTUSSIS and *B. parapertussis** are generally considered to be closely related. Eldering and Kendrick[1, 2] and Bradford and Slavin,[3] in 1937, first reported isolation of the species, *B. parapertussis.* By means of agglutination and agglutinin absorption, they showed *B. parapertussis* and *H. pertussis* to be related but not identical. Subsequent work by Flosdorf, Dozois, and Kimball[4] confirmed these findings that cross agglutination occurs between *B. parapertussis* and *H. pertussis* in phase I. It was shown further[5] that phase I *H. pertussis* and *B. parapertussis* each contain two toxins, one thermolabile[6] and the other thermostable, and that these two toxins in both organisms are antigenically similar.

Miller and co-workers[7] have reported that agglutinins for *B. parapertussis* are rather widespread in the sera of children in California. We have found these agglutinins to be prevalent in the sera of children and adults in the East. The sera studied fall into three groups: those in which there are no agglutinins for either *B. parapertussis* or phase I *H. pertussis,* those in which there are agglutinins for both, and those in which agglutinins are found for *B. parapertussis* with virtually none versus *H. pertussis* in phase I. In only two sera have agglutinins been found for phase I *H. pertussis* and not for *B. parapertussis.*

The question naturally arises as to whether the prevalence of agglutinins for *B. parapertussis* could conceivably be the result of nonspecific stimulation. It is possible that the parapertussis agglutinins could be present either as a result of specific infection with *B. parapertussis* or as a result of whooping cough due to *H. pertussis,* inasmuch as there is some agglutinative cross reaction between the two organisms. It is striking that such a high incidence of agglutinins for parapertussis exists when only occasional clinical cases of whooping cough due to *B. parapertussis* have been reported in the literature. Furthermore, when these cases have occurred they have not appeared to be clinically serious. This suggests the possibility that *B. parapertussis* generally does not

From the Departments of Bacteriology and Pediatrics, University of Pennsylvania, and the Children's Hospital of Philadelphia.

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*As previously discussed,[4] there is not yet general agreement with respect to classification of *B. parapertussis.*

cause a serious disease and that infection with it might be rather widespread without being generally recognized clinically.

In our earlier work the antigenic relationship of the two organisms was not investigated by means of cross-absorptive experiments, because in our hands spontaneous agglutination of *B. parapertussis* made the results unreliable. Recently we have found that the use of sodium chloride in a concentration of 1.7 per cent prevents spontaneous agglutination, and satisfactory, clean-cut results can be obtained. It has seemed worth while, therefore, to pursue a little further the comparative antigenic analysis of the two organisms, particularly in view of the incidence of parapertussis agglutinins in the general population.

METHOD

Absorption of sera was carried out as published previously[8] with the exception of the use of 1.7 per cent sodium chloride so as to have that as the final concentration in all agglutination tests with *B. parapertussis* as antigen. Both species were grown on Bordet-Gengou medium* for seventy-two hours. The bacterial cells were harvested in 0.85 per cent sodium chloride solution, centrifugalized, and washed once. The *H. pertussis* cells to be used as testing antigen in agglutination were resuspended in distilled water, the *B. parapertussis* cells in 1.7 per cent sodium chloride. All subsequent serum dilutions were made with 1.7 per cent sodium chloride. Equal quantities of diluted serum and pertussis antigen gave the usual final sodium chloride concentration of 0.85 per cent.

Rabbit sera prepared against phases I, III, and IV *H. pertussis* and against *B. parapertussis* as well as various human sera were absorbed in this way with both species and tested by agglutination with each species. Normal adult sera showing agglutination against both organisms and against only *B. parapertussis* were studied. The sera of children who had been vaccinated by standard procedure with killed whole phase I *H. pertussis* cells as well as with sera of adults who had been hyperimmunized[9] with the same vaccine were also studied. In order to determine whether or not comparative results would be representative of each of these species, strains of each collected from various other workers throughout this country were studied.

All of the results reported in this paper include only those from a single absorption. Consequently the high titer phase I serum was not completely absorbed by phase I organisms; these homologous agglutinins, however, can be completely removed by three successive absorptions. A single absorption with phase I organisms was sufficient, however, to remove the heterologous agglutinins. The agglutinins against *B. parapertussis* in serum versus *B. parapertussis* were removed readily by a single absorption with the homologous organisms.

The agglutinative titer of adults against *H. pertussis* and *B. parapertussis* before and after step-up doses of typhoid vaccine in previously

*The blood used for this work was kindly supplied by Sharp & Dohme.

vaccinated individuals and an experimental influenza virus type A vaccine was determined in order to obtain some evidence as to whether or not the titer against *B. parapertussis* might be increased nonspecifically. No nonspecific increase in agglutinative titer was observed. Increase in agglutinative titer against *B. parapertussis*, however, as well as against phase I *H. pertussis* was found following vaccination of children with killed phase I cells. Similarly, an increase in titer against both organisms was found after skin testing[10] with the purified agglutinogen of phase I *H. pertussis* cells. All of these sera were also tested by absorption, as shown later.

RESULTS

The results in Table I indicate that the incidence of agglutinins versus *B. parapertussis* is rather generally widespread. Inasmuch as this is a similar observation to that reported by Miller for the West Coast, it is probable that it is a rather general phenomenon in this country. The data show further that the incidence increases with age during general urban contact as contrasted with institutional sheltering.

TABLE I

INCIDENCE OF AGGLUTININS AGAINST *H. pertussis*, PHASE I, AND *B. parapertussis*

	URBAN†				INSTITUTIONAL§			
	ADULTS		CHILDREN‡		ADULTS		CHILDREN‡	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Positive to *B. parapertussis*	146	91	17	61	37	74	20	20
Positive to phase I *H. pertussis*	73	45	19	68	27	54	26	26
Positive to both	68	42	13	46	21	42	12	12
Negative* to both	11	7	6	21	8	16	59	58
Total in group	161	100	28	100	49	100	101	100

*Titer less than 1:20.

†The persons in this group are from Philadelphia.

‡Two to 12 years old.

§Most of the individuals represented in this group have led a continuous institutional life since preschool age. Some of the adults entered the institution at late adolescence. The children are from children's hospitals and the adults from state institutions located in New Jersey, Pennsylvania, and Massachusetts.

The results of absorption of immune rabbit serum versus *H. pertussis*, phase I, and of rabbit serum versus *B. parapertussis* by homologous and by heterologous organisms, as summarized in Table II, indicate that either organism absorbs from its homologous antiserum agglutinins both against itself and against the heterologous species. On the other hand, either organism can absorb from the heterologous serum only the agglutinins against itself. These results with rabbit sera are in agreement with those of Bradford and Slavin[3] and Eldering and Kendrick.[2]

The results of agglutinin absorption of the rabbit sera indicate the presence of a minor antigen common to phase I *H. pertussis* and *B. parapertussis*. The agglutinins versus this minor antigen may be absorbed by either species from either homologous or heterologous anti-

TABLE II

RESULTS OF SINGLE ABSORPTION OF IMMUNE RABBIT SERA VERSUS *H. pertussis* AND *B. parapertussis**

SERUM VS.	ANTIGEN		AGGLUTINATION TEST (FINAL SERUM DILUTION)									
	ABSORBING	TEST	160	320	640	1,280	2,560	5,120	10,240	20,480	40,960	81,920
Phase I *H. pertussis*	Sodium chloride	Phase I pertussis	4	4	4	4	4	4	4	4	3	1
		Parapertussis	4	4	4	1	0	0	0	0	0	0
	Phase I† H. pertussis	Phase I pertussis	4	4	4	3	1	Tr.	0	0	0	0
		Parapertussis	0	0	0	0	0	0	0	0	0	0
	B. parapertussis	Phase I pertussis	4	4	4	4	4	4	4	4	3	Tr.
		Parapertussis	0	0	0	0	0	0	0	0	0	0
B. parapertussis	Sodium chloride	Phase I pertussis	4	4	4	2	Tr.	0	0	0	0	0
		Parapertussis	4	4	4	4	4	4	4	4	2	Tr.
	Phase I H. pertussis	Phase I pertussis	1	Tr.	0	0	0	0	0	0	0	0
		Parapertussis	4	4	4	4	4	4	4	4	3	1
	B. parapertussis	Phase I pertussis	1	Tr.	0	0	0	0	0	0	0	0
		Parapertussis	1	0	0	0	0	0	0	0	0	0

*Similar results were obtained with two different strains of *H. pertussis* and three different strains of *B. parapertussis* and their corresponding antisera.

†Three absorptions are necessary for complete removal of homologous agglutinins by phase I cells from high titer phase I immune serum. This is not the case with any of the other three combinations.

serum. Therefore, when agglutinins versus *B. parapertussis* in an unknown serum are found to be absorbed by phase I *H. pertussis*, they are thereby shown to be agglutinins versus this common minor antigen and therefore not present as a result of specific antigenic stimulation by *B. parapertussis*. On the other hand, when the parapertussis agglutinins are removed only by absorption with *B. parapertussis*, specific antigenic stimulation with *B. parapertussis* must have occurred.

TABLE III

RESULTS OF SINGLE ABSORPTION OF HUMAN ADULT SERUM WITH *H. pertussis* AND *B. parapertussis*

SERUM	ANTIGEN		AGGLUTINATION TEST (FINAL SERUM DILUTION)						
	ABSORBING	TEST	40	80	160	320	640	1,280	2,560
No. 50, normal adult	Sodium chloride	Phase I	4	3	Tr.	0	0	0	0
		Parapertussis	4	4	4	4	2	1	0
	Phase I	Phase I	1	1	0	0	0	0	0
		Parapertussis	4	4	4	4	Tr.	0	0
	Parapertussis	Phase I	0	0	0	0	0	0	0
		Parapertussis	0	0	0	0	0	0	0
No. 45, normal adult	Sodium chloride	Phase I	4	4	4	2	Tr.	0	0
		Parapertussis	4	4	4	4	2	0	0
	Phase I	Phase I	2	0	0	0	0	0	0
		Parapertussis	2	1	Tr.	0	0	0	0
	Parapertussis	Phase I	4	4	4	3	1	0	0
		Parapertussis	0	0	0	0	0	0	0
Pool of adult hyperimmune serum, lot 150C	Sodium chloride	Phase I	4	4	4	4	4	2	Tr.
		Parapertussis	4	4	4	4	4	1	0
	Phase I	Phase I	Tr.	0	0	0	0	0	0
		Parapertussis	3	1	1	0	0	0	0
	Parapertussis	Phase I	4	4	4	4	4	3	0
		Parapertussis	0	0	0	0	0	0	0

Agglutination with the normal adult sera following absorption with each of the two species, as shown in Table III, indicates that the presence of parapertussis agglutinins may be the result of stimulation either by *B. parapertussis* itself or by phase I *H. pertussis*. The normal adult serum No. 50 agglutinates both phase I and *B. parapertussis* cells, but the absorptive tests indicate that this agglutination is the result of specific *B. parapertussis* stimulation. Absorption with phase I organisms removes some of the homologous agglutinin but very little of the heterologous. Absorption with *B. parapertussis*, however, prevents the agglutination of both down to a 1:40 dilution of the serum. Serum No. 45, on the other hand, contains agglutinins specific for each species, although the indication is that the phase I agglutinins predominate.

The absorptive tests with the pooled hyperimmune serum give results similar to those with the No. 45 normal adult serum, except of course, the titer of the unabsorbed serum is higher. These results indicate that the high titer of the agglutination of both organisms is the result

TABLE IV

RESULTS OF SINGLE ABSORPTION OF HUMAN SERUM WITH INCREASED TITER RESULTING FROM SKIN TEST

SERUM	TIME OF BLEEDING	ANTIGEN		AGGLUTINATION TEST (FINAL SERUM DILUTION)								
		ABSORBING	TEST	40	80	160	320	640	1,280	2,560	5,120	10,240
D. F., vaccinated child	Before skin test	None	Phase I	4	4	4	4	4	4	3	0	0
			Parapertussis	4	4	3	3	1	0	0	0	0
	After skin test	Sodium chloride	Phase I	4	4	4	4	4	4	4	2	0
			Parapertussis	4	4	4	4	4	4	3	0	0
		Phase I	Phase I	1	0	0	0	0	0	0	0	0
			Parapertussis	3	1	Tr.	Tr.	0	0	0	0	0
		Parapertussis	Phase I	4	4	4	4	4	3	Tr.	0	0
			Parapertussis	0	0	0	0	0	0	0	0	0
J. F., vaccinated child	Before skin test	None	Phase I	4	4	4	4	4	4	3	0	0
			Parapertussis	Tr.	0	0	0	0	0	0	0	0
	After skin test	Sodium chloride	Phase I	4	4	4	4	4	4	4	4	1
			Parapertussis	4	4	2	1	1	Tr.	0	0	0
		Phase I	Phase I	1	0	0	0	0	0	0	0	0
			Parapertussis	1	0	0	0	0	0	0	0	0
		Parapertussis	Phase I	4	4	4	4	4	4	4	4	1
			Parapertussis	0	0	0	0	0	0	0	0	0
H. F., normal adult	Before skin test	None	Phase I	1	Tr.	0	0	0	0	0	0	0
			Parapertussis	Tr.	0	0	0	0	0	0	0	0
	After skin test	Sodium chloride	Phase I	4	4	4	3	1	Tr.	0	0	0
			Parapertussis	4	4	4	3	1	0	0	0	0
		Phase I	Phase I	Tr.	Tr.	0	0	0	0	0	0	0
			Parapertussis	3	1	0	0	0	0	0	0	0
		Parapertussis	Phase I	4	4	4	2	Tr.	0	0	0	0
			Parapertussis	0	0	0	0	0	0	0	0	0
E. F., normal adult	Before skin test	None	Phase I	Tr.	0	0	0	0	0	0	0	0
			Parapertussis	2	1	Tr.	0	0	0	0	0	0
	After skin test	Sodium chloride	Phase I	4	4	4	4	2	Tr.	0	0	0
			Parapertussis	4	2	Tr.	0	0	0	0	0	0
		Phase I	Phase I	Tr.	Tr.	0	0	0	0	0	0	0
			Parapertussis	4	2	Tr.	0	0	0	0	0	0
		Parapertussis	Phase I	4	4	4	4	3	1	0	0	0
			Parapertussis	0	0	0	0	0	0	0	0	0

of stimulation by phase I vaccination. The residual parapertussis agglutination remaining after absorption with phase I strains, but which is taken out by *B. parapertussis*, is probably the result of the *B. parapertussis* agglutinins which the adults had prior to their immunization with phase I vaccine of whole killed phase I organisms. The adults represented by this pool are from a distribution of the population similar to that of the urban normal adult population of Table I.

Results in Table IV, with the vaccinated children, indicate that in the case of D. F., skin testing[10] with phase I purified agglutinogen has increased the titer of agglutination versus both species. Neither species, however, is able to absorb the heterologous agglutinins completely, indicating that some parapertussis agglutinins probably were present prior to vaccination and skin testing. The increase in titer versus *B. parapertussis* undoubtedly was due to the content of the common minor antigen in the purified agglutinogen. On the other hand, in the case of J. F., although the agglutinative titer versus both species was increased as a result of skin testing, both the homologous and heterologous agglutination could be removed almost completely by absorption with phase I organisms; by absorption with *B. parapertussis*, only the parapertussis agglutination could be absorbed. Parapertussis agglutinins probably were not present prior to vaccination.

The results, as shown in Table IV, of absorption of adult serum obtained after the skin testing with purified phase I agglutinogen, indicate that again both homologous and heterologous agglutination titer is increased as a result of skin testing. Neither species is able to absorb completely the heterologous agglutinin, indicating that major agglutinins versus both species are present. Once again, however, the titer versus both species had been increased as a result of the skin testing with purified phase I agglutinogen; the increase in agglutination versus *B. parapertussis* as a result of skin testing occurred, no doubt, through the agency of the common minor antigen.

TABLE V

SUGGESTED SIMPLEST AGGLUTINOGENIC STRUCTURE OF *H. pertussis* AND *B. parapertussis*

PHASE OR SPECIES	STRAIN	ANTIGENS†
I	Probably all	A, b, c, e
II*	?	Y, Z
III	538	B, c, z
III	588	B, d
IV	Probably all	D, c, f
B. parapertussis	All	P, e, f

*Based on results of Leslie and Gardner;[13] we have never located a phase II strain.

†Antigens indicated in capital letters are major in the phase or species indicated; the others are present either in small amount or are deep-seated or both. The apparent deep-seated location of "c" in phase I strains explain their failure to be agglutinated by phase III antisera, even though phase III organisms are agglutinated by phase I antisera; some "c" must exist in the phase I organisms to elicit formation of the corresponding antibodies. The arrangement of symbols indicated is in simplest form; it would require further elaboration to explain minor differences in strains observed within a given phase or phase X.[4]

Cross agglutination reactions between *B. parapertussis* and phase III *H. pertussis* failed to show any relationship between the two organisms. However, cross agglutination and agglutinin absorption tests between *B. parapertussis* and phase IV *H. pertussis* showed the presence of still another common antigen in these two organisms. This relationship, as shown in Table V, is discussed later.

DISCUSSION

The results seem to indicate rather clearly that cross agglutination between the two species of organisms is the result of a common minor antigen and, accordingly, the table previously reported[4] for the suggested simplest agglutinogenic structure of *H. pertussis* may be extended to include *B. parapertussis*. This is done in Table V. Another common minor antigen explains the slight degree of cross reaction between phase IV *H. pertussis* and *B. parapertussis* cells. All of these common antigens seem to be present in small amount or seem to be deep seated. It is particularly interesting that the purified agglutinogen as a result of skin testing is able to cause a marked increase in agglutination titer versus *B. parapertussis*. This purified reagent has also been found to have the property of absorbing phase I agglutinins out of rabbit sera versus *B. parapertussis* and also the parapertussis agglutinins from sera versus phase I *H. pertussis*. Absorption of immune rabbit sera versus *B. parapertussis* with the purified material, however, does not cause any reduction in parapertussis agglutination. This indicates definitely that the purified phase I agglutinogen contains the common minor antigen; this could be, of course, either as a single chemical group on a single phase I agglutinogenic molecule, or the common minor antigen could be present as a molecular impurity in the phase I preparation.

A further interesting point in connection with the difference between *B. parapertussis* and phase I *H. pertussis* is in the chemical properties of the agglutinogen derived in purified form from the two species. The phase I material is soluble in distilled water in the absence of salt at all pH values; on the other hand, the parapertussis agglutinogen precipitates at pH 4.5 unless there is salt present in approximately 1 per cent concentration.[11] It is suggested that this chemical property of the parapertussis agglutinogen is responsible for the spontaneous agglutination of *B. parapertussis* cells at salt concentrations less than twice isotonic. Also, it is rather interesting that the electron microscope shows a difference in the morphology of *B. parapertussis* and phase I *H. pertussis* cells.[12]

With regard to the clinical significance of the serologic findings, it must be pointed out that very little is known about the nature of the typical disease of parapertussis. The "severe cases" seem to be similar to mild cases of whooping cough, but the number of such severe cases which have been observed, with bacteriologic diagnosis, is insufficient

to account for the wide incidence of agglutinins specific for *B. parapertussis* in the general population. This wide incidence, however, does seem to suggest, perhaps, that there is some prevalent mild disease in children which is specifically related to *B. parapertussis* but which is not ordinarily etiologically diagnosed. Further clinical investigation will be required in order to determine the full significance of the incidence of agglutinins specific for *B. parapertussis.*

For practical purposes, there is the question of whether or not agglutinins for the common minor antigen can be effective in cross protection against either *H. pertussis* or *B. parapertussis.* It might well be that such agglutinins could be present in sufficient concentration to provide cross protection, but as a result of natural disease, it appears that the agglutinins versus the common antigen are not present in high enough titer. This could explain the apparent lack of cross protection afforded by an attack of one disease against the other. On the other hand, as a result of intensive immunization either in rabbits or in man in the production of hyperimmune serum, the agglutinative titer versus the common minor antigen reaches a high value. It might well be that hyperimmune serum could yield cross protection, but this also is a matter which will require clinical investigation.

The remarkable increase in agglutinative titer following skin testing with purified phase I agglutinogen,[10] even as in the case of E. F. (Table IV), in the absence of circulating antibodies at the time of the test (but presumably fixed antibodies are present) is interesting. It suggests such skin testing could serve both as a test for susceptibility to whooping cough and as a stimulating vaccination. This would be performed at say six to twelve months following primary vaccination. Whether the stimulation of antibodies versus the common minor antigen is sufficient to protect against parapertussis requires investigation.

SUMMARY

1. Cross agglutination between *B. parapertussis* and *H. pertussis* in phase I has been shown by means of absorptive tests to be due to a common minor antigen.

2. The findings of Miller have been confirmed with respect to a general wide incidence of parapertussis agglutinins among the general population. By means of agglutinin absorption, it has been shown that these agglutinins for *B. parapertussis* are specific in large measure, presumably as a result of specific infection by *B. parapertussis,* and are not the result of the common minor antigen which exists in both *B. parapertussis* and *H. pertussis.*

Incidence of agglutinins for *B. parapertussis* in both children and in adults in two institutions, has been found to be lower than in the general population. In the general population, the incidence found has increased with age.

3. As a result of intensive immunization of either man or animals, the agglutinative titer versus the heterologous species is increased through the agency of the common minor antigen, but it is not known whether such agglutinins are effective in clinical cross protection against either disease. Skin testing for susceptibility to whooping cough with purified agglutinogen also stimulates production of these same agglutinins as well as those versus the major phase I antigen.

4. The use of purified agglutinogen as an intradermal reagent for stimulation of immunity, as well as in skin testing for susceptibility to whooping cough, is suggested.

5. The results of the present study suggest that only the relatively serious cases of parapertussis are diagnosed clinically and that these are similar to mild cases of whooping cough; the nature of the typical disease of parapertussis apparently is not recognized clinically in relation to the specific etiologic agent.

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A SERIES OF SUBSTITUTES FOR MILK IN THE TREATMENT OF ALLERGIES

LEON Z. WOLPE, M.D., AND PAUL C. SILVERSTONE
LOS ANGELES, CALIF.

ECZEMA has long comprised a series of trials and tribulations for every practitioner. Despite an understanding of the therapeutic fundamentals involved, even the expert frequently fails to produce desired results. Because of the prominent place of milk allergy,[1, 2] especially in the eczema of infancy, there have been evolved a series of milk substitutes prepared from soybean,[3-6] almond-vegetable[7] combinations, vegetable mixtures,* and lately hydrolyzed casein with brewer's yeast.[8] Both the almond-vegetable and vegetable mixtures have disappeared from the group of easily available substitutes. The fact that both included such a wide variety of allergenic possibilities probably accounted, in part, for their lack of popularity.

The soybean as a rich source of minerals, vitamins, proteins, and fats seemed an excellent basis for the construction of an effective formula. Yet, the majority of doctors who have employed soy in its various forms attest to the fact that it is an extremely potent allergen to which sensitivity may be apparent on first use or soon acquired after use. The most recent and radically different substitute[8] was reviewed by Hill, who concluded, with regard to this preparation, "it is possible to feed infants satisfactorily for periods of at least three months," and further that "no milk-free food at present available is entirely without disadvantages. It is desirable to have more than one type of food in order to meet the individual needs of different babies."

Because of extensive individual variation in degree of sensitivity, reduction in any formula combination of the actual number of allergenic ingredients, as well as a wide flexibility in their separate amounts, according to the specific requirement, is extremely important to the doctor. The work of several men[9] has demonstrated the diminished anaphylactogenicity of evaporated milk. Powdered milks, superheated in their preparation, are also less potent allergens. Precoagulation and predigestion, as seen in buttermilk and through rennin action in chymogen, both tend to diminish anaphylactogenicity.

The antigenic power of casein is not diminished by heat.[10] The casein of both cow's milk and goat's milk are almost immunologically identical.[11] Therefore, in a casein-sensitive infant, changing from one to the other, whether superheated or not, the allergen remains. Cow's milk

*Cemac (Mead Johnson & Co.).

contains three times more casein than lactalbumin. Thus we have a four times greater chance by using cow's milk, rather than human milk, to sensitize to this antigenic fraction.

In seventy-five eczematous infants checked by Hill and Pratt,[10] 6.7 per cent were sensitive to casein alone, 46.6 per cent to both casein and lactalbumin, and 46.6 per cent to lactalbumin alone. Milk sensitivity, then, may be divided into three classifications:[11] (1) species-specific factor of cow lactalbumin; (2) common factor to both cow and goat lactalbumin; and (3) casein. In the first group, changing to goat's milk is indicated. In the second group, changing to goat's milk may offer some degree of improvement. In the third group, goat's milk is valueless. In another paper,[1] Hill states "one wishes that goat's milk were consistently a cure for eczematous infants with milk sensitivity. Unfortunately, it is only occasionally so. For all these reasons, as well as from a considerable practical experience, we prefer to do away with milk entirely if milk sensitivity exists and if the eczema is of any severity, provided, always, that the infant is in a good state of nutrition."

In 1929 Hill and Stuart used a flour made from pressed soybean cake (i.e., residue from soybean after extraction of oil) to which were added barley flour, olive oil, sodium chloride, and calcium carbonate.* In 1933 Stearns investigated the nitrogen, calcium, and phosphorus metabolism of two children fed such a mixture and considered the retention of calcium and phosphorus unsatisfactory, but found the relative retentions of nitrogen, calcium, and phosphorus improved by substituting dicalcium phosphate for calcium carbonate. In the same year, 1933, Blackfan and Wolbach recorded the development of keratomalacia in a 6-month-old infant fed on it. In 1935 Rittinger and his colleagues used a dry-ground flour with or without partial breast feeding. The infants' weight curves paralleled the Holt line for the most part. In 1938 Chang and Tso fed forty-nine babies on a mixture of hand-ground flour made from roasted beans with sugar, starch, calcium lactate, and salt. They considered their results satisfactory despite a few failures.

The comprehensive survey of soybean chemistry by Mackay[3] makes the reader realize the tremendous variation in the available protein and fat of soy formulas due to a multiplicity of factors such as mode of preparation and degree and type of heating of the beans before the flour is obtained as well as the method of treatment of the flour before actual incorporation into the formula. The percentage of available protein may vary from 8 to 58 per cent, the percentage of fat from a negligible amount to 18 per cent. Any formula directing the patient to use merely "soy flour" without complete investigation into the manufacture of this flour is subjecting the formula composition to variations which may be enormous. The employment of any calcium preparation without phosphorus in combination likewise may lead to false values,

*Sobee (Mead Johnson & Co.).

since the phosphorus content of the soybean flour varies in similar manner. The fact that keratomalacia has occurred with such a feeding and studies of nitrogen, calcium, and phosphorus metabolism have proved unsatisfactory should obviate the use of an unknown flour or one used with any but calcium-phosphorus addition.

The preparation of soy flour of choice is the Berczeller process[3] which was devised to obtain a commercial flour of high fat content and good keeping quality devoid of unpleasant strong taste. The beans are cleaned, subjected to the action of saturated steam from ten to fifteen minutes, dried, and cracked to remove the husks. The germ is removed in this process. The flour is then subjected to steam distillation which removes some of the volatile material responsible for the bitter taste.

Bain[12] says, concerning various proprietary milk substitutes, "in the treatment of infantile eczema, these products have marked a definite advance. Their expense makes them prohibitive in many cases. What we need is a milk substitute, which is cheap, palatable, and easily prepared at home, and which meets the food requirements of the infant."

Cereals and vegetables of various types[13-17] are obtainable throughout the world. Beginning with a knowledge of their individual analyses, then fortifying them with dextrose, gelatin, and oil (cottonseed, olive, sesame, corn, peanut, soy), the authors have attempted to construct a series of formulas with the following characteristics:

1. Correct chemical constitution
   a. Amino acids, calcium, phosphorus, iron[13] (optimal calcium-phosphorus ratio, 1:1 to 2:1).
      Daily minimum intake: calcium, 1 Gm.; phosphorus, 1.3 Gm.; iron, 10 mg.
   b. Carbohydrate, protein, fat (optimal balance and caloric value, 700 to 1,000 calories daily).
2. Correct physical constitution
   a. Surface tension (approximating milk)
   b. Curd tension (soft curd level)
   c. pH (neutral or slightly acid)
3. Palatability
4. Fluidity
5. Low cost
6. Ease of availability
7. Ease of preparation

The following flours have been used as bases for milk substitutes: oat, barley, soy, lima bean, pea, taro, rice, rye, and corn. Table II designates the amounts of the several ingredients used to constitute two quarts of diluted formula. Formulas were prepared every other day, alternating constantly between two flours. The oil of choice has been olive oil.[18] If specific sensitivity to it or to the flour was observed, appropriate changes were made. The formulas were simmered in a covered double boiler for two hours, until clinical evidence of eczema in the patients had subsided; then cooking time was reduced to fifteen or twenty

TABLE I

ANALYSIS OF CONSTITUENTS*

CONSTITUENT	PROTEIN (PER CENT) ‡	FAT (PER CENT)	CARBOHYDRATE (PER CENT)	ASH (PER CENT)	CALCIUM (PER CENT)	PHOSPHORUS (PER CENT)	IRON (PER CENT)	COPPER (PER CENT)	SODIUM (PER CENT)	POTASSIUM (PER CENT)	SULFUR (PER CENT)	CHLORINE (PER CENT)	MAGNESIUM (PER CENT)
Barley†	10.5	2.2	72.8	2.6	0.051	0.40	0.0048	0.0008	0.076	0.48	0.15	0.016	0.14
Corn	9.2	1.9	75.4	1.5	0.016	0.15	0.0009	0.0002	0.039	0.21	0.11	0.15	0.084
Lima bean	18.1	1.5	65.9	3.8	0.071	0.39	0.116	0.0086	0.25	1.74	0.16	0.026	0.19
Oat	16.0	6.8	65.6	2.1	0.065	0.39	0.0048	0.0005	0.062	0.34	0.20	0.069	0.11
Pea	24.6	1.0	62.0	3.0	0.033	0.27	0.0054	0.0014	0.104	0.90	0.22	0.035	0.15
Poya meal	0.5	2.0	76.5	–	0.1	0.15	0.0050	0.0002	–	–	–	–	–
Rice	7.9	0.3	79.0	4.1	0.065	0.34	0.0020	0.00014	0.025	0.070	0.12	0.054	0.033
Rye	13.1	2.0	73.9	1.5	0.061	0.39	0.0039	0.00042	0.035	0.45	0.17	0.023	0.13
Soybean	39.2	17.4	28.0	4.8	0.235	0.67	0.0067	0.0012	0.018	0.88	0.54	0.019	0.25
Gelatin	88.5	0	0	1.2	0.435	0.23	0	0.0005	0	0	0	0	0
Cottonseed oil	0	100	0	0	–	–	–	–	0	0	0	0	0
Olive oil	0	100	0	0	–	–	–	–	0	0	0	0	0
Dextrose (C. P.)	0	0	100	0	0	0	0	0	0	0	0	0	0
Dextrose (U. S. P.)	0	0	92	0	0	0	0	0	0	0	0	0	0
Cane sugar	0	0	99.5	0	0	0	0	0	0	0	0	0	0
Cow's milk	3.3	4.8	4.8	0.7	0.118	0.093	0.00029	0.00002	0.051	0.14	0.034	0.106	0.012
Human milk	1.4	3.7	7.4	0.2	0.034	0.015	0.00018	0.00002	0.01	0.047	0.001	0.035	0.005

TABLE I—CONT'D

CONSTITUENT	FIBER (PER CENT)	FIXED BASE (PER CENT)	IODINE NO. OF FATS	ACID NO. OF FATS	OLEIN (PER CENT)	I_2 PARTS/ BILLION	TABLE-SPOONS PER OUNCE	COST PER OUNCE	COST PER TABLESPOON	KG. CAL. PER OUNCE
Barley	6.5	0.75	113.5	29	26.5	73	5¼	$0.00923	$0.00179	100
Corn	1.7	0.35	119.9	2.5	44.8	52	4¼	0.00938	0.0022	100
Lima bean	3.8	2.2	–	–	–	50	4½	0.00938	0.00208	99.1
Oat	1.4	0.58	114.2	–	34.7	100 (ave.)	3½	0.00938	0.00268	98.0
Pea	5.4	1.19	–	–	–	50 (ave.)	4	0.00938	0.00234	100
Poya meal	–	–	–	–	–	–	2½	0.0466	0.0186	107
Rice	10.4	0.193	99.9	73.7	41.0	20	4½	0.00938	0.00208	99.4
Rye	2.1	0.68	81.9	4.1	–	3	5½	0.00938	0.0017	99.3
Soybean	4.6	1.4	130	1.3	33.4	0	6¼	0.00938	0.0015	97.2
Gelatin	0	0	–	–	–	–	3⅓	0.055	0.0165	104
Cottonseed oil	0	0	103	0.6	35.2	0	2⅛	0.0122	0.00563	270
Olive oil	0	0	83	0.7	84.4	66	2⅛	0.0122	0.00563	270
Dextrose (C. P.)	0	0	–	–	–	–	2.5	0.0431	0.0172	191
Dextrose (U. S. P.)	0	0	–	–	–	–	3.0	0.0059	0.00198	176
Cane sugar	0	0	–	–	–	–	2.6	0.0014	0.00054	191
Cow's milk	0	0.32	28.5	2.05	34.6	100	–	–	–	–
Human milk	0	0.096	54	1.8	–	43	–	–	–	–

*Values were compiled from data given in references 49 to 56 inclusive.
†Whole grains.
‡Per cents by weight.

TABLE II

SUGGESTED FORMULAS

NO.	CONSTITUENT	PER CENT OF EACH BY WEIGHT	DRY FORMULA			DILUTED FORMULA			DILUTION IN PARTS OF EACH		QUANTITIES OF EACH ADD WATER TO TWO QUARTS TOTAL		
			PROTEIN (PER CENT)*	FAT (PER CENT)	CARBOHYDRATE (PER CENT)	PROTEIN (PER CENT)	FAT (PER CENT)	CARBOHYDRATE (PER CENT)	FORMULA	WATER	CUPS	TBSP.	TSP.
2 B	Poya meal†	25	14.8	19.2	60.5	2.7	3.5	11.0	1	4½		7	
	Dextrose	41.4										9¾	
	Gelatin	14.6										5¾	
	Oil	19.0										4¾	
	Bone phosphate or dicalcium phosphate												2¼ 4
						Add 1 tsp. vanilla 1 tsp. salt 1 gr. saccharin 13 drops of 10 per cent ferric chloride solution							
6 B	Oat flour	35.4	21.1	18.4	55.2	3.2	3.0	8.3	1	5.6		12	
	Dextrose	32.0										6¾	
	Gelatin	12.4										4¼	
	Oil	20.1										4¼	
	Bone phosphate or dicalcium phosphate												4 7½
						Add 1 tsp. vanilla 1 tsp. salt 1 gr. saccharin 12 drops of 10 per cent ferric chloride solution							
10 C	Barley flour	21.4	18.3	23.1	53.4	3.1	3.9	9.1	1	4.87		11	
	Dextrose	37.8										7¾	
	Gelatin	18.3										6	
	Oil	22.6										5	
	Bone phosphate or dicalcium phosphate												4½ 8
						Add 1 tsp. vanilla 1 tsp. salt 1 gr. saccharin 13 drops of 10 per cent ferric chloride solution							
15 A	Rye flour	60	18.5	19.2	54.4	3.4	3.5	9.9	1	4½	2	1	
	Dextrose	10										2	
	Gelatin	12										4	
	Oil	18										4	
	Bone phosphate or dicalcium phosphate												3½ 6¼
						Add 1 tsp. vanilla 2 tsp. salt 2 gr. saccharin 7 drops of 10 per cent ferric chloride solution							

16 B	Lima bean Dextrose Gelatin Oil Bone phosphate or dicalcium phosphate	32 35 15 18	19.1	18.8	56.1	3.2	3.1	9.3	1	5	¾	2¾ 7¼ 5.0 4	 4.0 7¼
						Add 1 tsp. vanilla 2 tsp. salt 9 drops of 10 per cent ferric chloride solution							
17	Dried peas Dextrose Gelatin Oil Bone phosphate or dicalcium phosphate	33 27 12 18	19.8	18.0	64	3.3	3.0	10.6	1	5		13 7¾ 4.0 4.0	 4.0 7¼
						Add 1 tsp. salt 12 drops of 10 per cent ferric chloride solution							
18	Soy flour Dextrose Oil Bone phosphate or dicalcium phosphate	46 42 12	18	20	54.9	3.0	3.3	9.1	1	5	1½	 8¼ 2¼	 3¼ 5¾
						Add 1 tsp. salt 10 drops of 10 per cent ferric chloride solution 1 tsp. vanilla							
19 B	Rice flour Dextrose Gelatin Oil Bone phosphate or dicalcium phosphate	35 27 20 18	20.5	18	55	3.4	3.0	9.1	1	5		15¾ 5¾ 6¾ 4	 4 7
						Add 1 tsp. salt 12 drops of 10 per cent ferric chloride solution 1 tsp. vanilla 1 gr. saccharin							
20 A	Corn flour Dextrose Gelatin Oil Bone phosphate or dicalcium phosphate	40 26 16 18	19.8	18.7	56.2	3.0	3.1	9.3	1	5	1	½ 5¼ 5 3¾	 4¼ 7½
						Add 2 tsp. salt 2 gr. saccharin 14 drops of 10 per cent ferric chloride solution 1 tsp. vanilla							
	Cow's milk Human milk	100 100				3.3 1.4	4.8 3.7	4.8 7.4					

*All percentages are by weight.
†All cereals are whole grain flours.

minutes. Despite the controversial opinions[3, 19-21] concerning the diminution of allergenicity by superheating, it was deemed safer to so treat the formulas at the beginning. Similarly, because of the work which has been done to show that protein which is superheated loses from 10 to 50 per cent of its value,[21] the period of simmering was reduced as soon as possible.

Form I is offered as a sample formula form given to the mothers as directions for home preparation of milk substitutes.

FORM I

	CUP	TBS.	TSP.	DROPS	GRAINS
Flour					
Gelatin (unflavored)					
Oil					
Saccharin					
Dextrose					
Salt					
Imitation vanilla					
Ferric Chloride (10 per cent solution)					
Vitamin powder	Measuresful dissolved in one bottle of formula daily. Add immediately before feeding.				

DIRECTIONS FOR MAKING FORMULA

1. Place the above ingredients in a double boiler. Gradually stir in two quarts of water. Stir continuously for the first fifteen minutes, then only occasionally; simmer for two hours. Then add boiled water to make up to two quarts again.
2. Pour ------ ounces into ------ bottles and fill all the bottles while formula is still hot.
3. Thirty minutes before feeding, heat the bottle by placing in a pan of hot water until the formula is liquid. Then cool to feeding temperature and test before offering.
4. Have the hole in the nipples large enough so the formula will drip one drop in two seconds.
5. Shake bottle before using. Add prescribed number of measures of vitamin powder at this time.
6. The filled formula bottles must be kept in a refrigerator at all times.

Form II comprises the instructions for care of the infant's room, not with regard to the immediate care of the skin but a precautionary measure, because of the allergic status, to help avoid future allergies.

FORM II

PREPARATION AND MAINTENANCE OF A DUST-FREE ROOM

1. The room should contain only one bed, preferably an iron one. If a second bed is in the room, it, too, must be prepared as will be described.

2. All the furniture, rugs, curtains, and drapes must be taken from the room, the clothes closet emptied (keep clothes elsewhere), and the room cleaned as follows:

3. Seal all furnace pipes leading into the room. Clean the walls and ceiling. Scrub the woodwork and the floors in the room and closets. Wax the floors.

4. Scrub the bed. Scrub the springs. Cover the mattress, pillows, and box springs, if used, with dust-proof slip covers. The encasings must be made of material which is not porous, or the dust will come through. The encasings must be sewed on, or otherwise closed up so they are completely air tight. This must be done outside of the cleaned room.

5. Set up the cleaned bed in the cleaned room, and on it place the cleaned or encased springs and the encased mattress. Make up the bed with the encased pillows and freshly washed bedding. Use washable blankets and washable bedspread. IMPORTANT: Do not use any kind of mattress pad on the bed.

6. A wooden chair which has been scrubbed may be used in this room. Rag rugs washed at least once a week may be used in this room. Plain light curtains, washed once a week, may be used on the windows.

7. This room must be cleaned once daily and given a thorough and complete cleaning once a week.

8. Dressing and undressing must be done outside this room. The room is for sleeping only.

9. Articles of furniture which may hold dust should be removed from the house. If this is not possible, such articles should be vacuum cleaned thoroughly every day, at a time when the patient is out of the house, then the house aired well. Do not keep toys which will accumulate dust in the room. Use only washable toys.

Form III summarizes in outline form the local therapy employed during the entire period of observation of each patient.

FORM III

LOCAL THERAPY

I. *Crusted, oozing type:*

1. Saturated boric acid compresses from forehead to mouth. To rest of body, potassium permanganate (1:4,000) compresses.

2. Compresses are applied for at least fifteen minutes at intervals of three hours. If possible, they should be applied continuously.

3. In removing crusts at each cleaning (every eight hours day and night), use mineral oil compresses for five minutes, then gently remove with forceps or slight rubbing.

4. In the interval, if scaling persists, 5 per cent sulfathiazole ointment may be used. If there is no scaling but only an inflamed surface, apply 2 per cent ichthyol in plain Lassar's ointment.

5. For otitis externa, crusts are first removed. Then canals are irrigated with warm boric acid solution and dried with sterile applicators.

II. *Dry eczema:*

1. Use 2 per cent crude coal tar in vaseline; if applied to face, use face mask.

2. If itching is not controlled with vaseline tar, 2 per cent crude coal tar in equal parts of acetone and collodion may be painted on four or five times daily.

3. Regardless of what is applied to skin, use arm splints and restrain to bed with pins.

4. Stockings if rash is present over thighs or legs.

5. If there are any moist spots, these areas are painted with copper sulfate, 0.3; zinc sulfate, 0.3; camphor water q.s. ad., 60.0 Areas are painted every four hours.

III. *Scalp crusting (cradle cap):*

1. Use 2 per cent sulphur precipitate, 2 per cent salicylic acid in vaseline (rubbed in scalp three times daily).
2. Mineral oil; soak for five minutes once daily, then
3. On third day scrub with soap and water.
4. Then ointment may be applied as above each day.

IV. *General directions:*

No soap or water for cleansing purposes except when specifically ordered. Cleanse skin with mineral oil occasionally.

The vitamin powder employed[13] contains per gram:

3,000 I.U. vitamin B_1	50 mg. vitamin C
3,000 gamma vitamin B_2	10 mg. nicotinic acid
2,000 gamma pantothenic acid	5,000 I.U. vitamin A
300 gamma vitamin B_6	1,000 I.U. vitamin D

It was prepared with the same synthetic vanilla flavor in the milk substitutes and, when dissolved in two or three ounces of formula, was taken well.

At current market prices (April, 1942) the retail cost of the included milk substitutes varies from ten to fourteen cents daily except for the Hawaiian taro substitute, which totals twenty-two cents. The vitamin powder, which is prepared by a local concern, costs at retail price seven cents daily.

The choice of gelatin as the protein fortification seemed singularly proper in view of both its nonanaphylactogenicity as well as the complementary distribution of essential amino acids when combined with the several formula constituents.[14] Joslin[22] points out a particularly low incidence of upper respiratory infections in a group of babies fed gelatinized milk as compared to cow's milk and acidified cow's milk. Certainly if there is any possibility of reducing the incidence of such infection in a group of infants so highly susceptible, it would be desirable. Elterich, Boyd, and Neff[23] point out that gelatin does not specifically accelerate growth but does increase the caloric intake.[24] Jackson, Sommer, and Rose[25] feel that gelatin as a sole source of protein is not a suitable source of nitrogen, even when supplemented with the missing amino acids, but state that about 50 per cent of the rats used in their experimentation weathered a 35 per cent gelatin diet and after periods of adjustment either maintained body weight or grew at varying rates. Perlman,[26] in using gelatin as a *complementary* source of protein rather than as the sole source, observed a slightly higher rate of growth in infants fed gelatin than in infants fed same diet without gelatin. In the light of these works, we believe that in the milk substitutes offered, the *complementary* nature of the included gelatin protein removes most of

the objections to its use. Certainly the metabolic evidence of increase in weight and stature of the infants reviewed bolsters this opinion.

In 1933 Hansen[27] advanced a new theory regarding eczema. Burr and Burr[28] had shown that rats kept on a fat-free diet developed a skin condition similar to infantile eczema. The blood of these rats and of infants with eczema showed a lower than normal amount of unsaturated fatty acids. Clinical results[29] in this direction have been disappointing, but concerning the absorption ratio of the various dietary fats it is of great interest to note that Frontali, in a series of experiments,[18] demonstrated that cow's milk fat contains about 70 per cent of tripalmitin and 30 per cent of triolein, while fat of human milk contains about 70 per cent of triolein and only 30 per cent of tripalmitin and tristearin. His observations led him to believe that if efficient utilization of the fat of human milk were due to its greater content of triolein, improved retention of the fat of cow's milk could be obtained with an increase of the proportion of triolein. This could be accomplished practically by substituting a vegetable oil rich in triolein, as for instance, olive oil, for the butter of cow's milk.* Frontali found no evident relation between the iodine index, index of saponification, and the percentage utilization. He found, similarly increased absorption ratios but to a lesser degree in those oils which contain a greater quantity of linolein, another unsaturated triglyceride with two double linkages. Cow's milk fat, which is rich in saturated triglycerides with a mixture of tripalmitin and tristearin, is utilized poorly.

Other vegetable oils, as cocoanut oil and cottonseed oil, were used in the feeding of infants by Rochwood and Swikes (1919) and by Holt, Sr., Courtney, and Fokes (1919), who proved that these oils could be substituted for butter, in a great measure, to provide more economically the needed fat ration. In 1937 Blatt and Harris substituted olive oil for butter in the feeding of infants, again confirming good results (increase of weight and stature). We have used interchangeably the above-mentioned oils according to the individual sensitivity encountered.

Alvarez,[30] in describing the unfortunate plight of allergic patients who must exist on an exaggeratedly restricted dietary, states that not only may they become bored with their narrow diet but by eating so much of the few foods and eating them so often, they are likely to become sensitized to them and be thrown onto starvation rations. He states "some time ago a patient like this, who was almost at the end of her rope and facing starvation, solved the problem by taking in rotation the foods to which she was only slightly sensitive. As all allergists know, there are many persons who can take a small amount of a harmful food at intervals without serious trouble, but if they are to eat larger amounts or particularly if they eat the food every day for several days, they get into serious trouble. The trick then is to eat each mildly harmful food once

*Olac (Mead Johnson & Co.).

TABLE III

PHYSICAL AND CHEMICAL CONSTANTS OF DILUTED FORMULA*

FORMULA NO.	CALORIES PER QUART	COST PER QUART	OZ. UNDILUTED FORMULA PER QT. DILUTED FORMULA	PER QUART DILUTED FORMULA USING BONE PHOSPHATE					PER QUART DILUTED FORMULA USING DICALCIUM PHOSPHATE					FIBER (PER CENT)	ASH (PER CENT)	FIXED BASE (PER CENT)	I_2 PARTS PER BILLION	TRI OLEIN (PER CENT)	I_2 NUMBER OF CEREAL FATS
				CALCIUM (GM.)	PHOSPHORUS (GR.)	IRON (MG.)	COPPER (MG.)	Ca:P RATIO FORTIFIED FORMULA	CALCIUM (GM.)	PHOSPHORUS (GM.)	IRON (MG.)	COPPER (MG.)	Ca:P RATIO FORTIFIED FORMULA						
Cow's milk	664	12		1.15	0.91	2.8	0.19	1.3						0	0.7	0.32	100	1.4	28.5
Human milk	625	-		0.31	0.14	1.7	0.18	2.3						0	0.2	0.10	0.43	2.6	54
Poya 2 B	990	22	5.7	2.1	1.3	10.3	0.10	1.6	1.7	1.4	1.2	0.10	1.2	-	-	-	-	-	-
Oat 6 B	850	11	4.7	1.9	1.3	10.6	0.32	1.5	1.6	1.3	2.2	0.32	1.2	0.076	0.135	0.003	5.4	1.2	114.2
Barley 10 C	870	11	5	2.1	1.3	10.6	0.26	1.6	1.7	1.4	1.5	0.26	1.3	0.24	0.13	0.027	2.7	1.4	113.5
Rye 15 A	700	10	5	1.6	1.3	10.5	0.44	1.3	1.3	1.3	3.5	0.44	1.0	0.23	0.18	0.075	0.33	1.2	81.9
Lima bean 16 B	810	14	5	2.4	1.3	11.5	4.0	1.8	1.5	1.4	5.2	4.0	1.2	0.20	0.23	0.12	2.6	1.1	-
Peas 17	800	13	5	1.8	1.3	10.7	0.74	1.5	1.5	1.3	2.3	0.74	1.2	1.8	1.1	0.40	16	6.5	-
Soy 18	780	10	4.7	1.5	1.3	11.1	0.73	1.2	1.3	1.3	4.1	0.73	1.0	0.35	0.37	0.23	0	1.2	130
Rice 19 B	770	14	4.85	1.9	1.3	10.3	0.41	1.5	1.6	1.3	1.9	0.41	1.2	0.60	0.27	0.011	1.2	1.1	99.9
Corn 20 A	770	13	4.85	2.0	1.3	10.8	0.40	1.6	1.6	1.3	1.0	0.40	1.2	0.11	0.13	0.023	3.5	1.1	119.9

TABLE III—CONT'D

FORMULA NO.	IODINE NO. OF COTTONSEED OIL	ACID NO. OF CEREAL FATS	ACID NO. OF COTTONSEED OIL	CURD TENSION (HILL)	SURFACE TENSION DYNES PER CM.		pH		PER CENT AMINO ACIDS BY WEIGHT IN DILUTED FORMULA†										
					TEMPERATURE (° C.)	SURFACE TENSION	TEMPERATURE (° C.)	pH	ARGANINE	CYSTINE	HISTIDINE	ISOLEUCINE	LEUCINE	LYSINE	METHIONINE	PHENYLALANINE	THREONINE	TRYPTOPHANE	VALINE
Cow's milk	-	2	-	20	31.1	47.8	30	6.5	0.110	0.031	0.050	0.33		0.18	0.080	0.11	-	0.043	0.231
Human milk	-	1.8	-	-	-	-	30	7.0	0.051	0.035	0.018	0.07		0.068	0.020	0.022	-	0.022	0.01
Poya 2 B	103	-	-	0	30.0	46.5	20	5.0	-	-	-	-		-	-	-	-	-	-
Oat 6 B	103	-	0.6	0	30.6	34.0	36	6.2	0.22	0.021	0.033	0.21		0.14	0.015	0.41	-	0.0068	0.0086
Barley 10 C	103	29	0.6	0	30.0	49.6	30	6.0	0.30	0.012	0.034	0.24		0.19	0	0.060	-	0.0030	0.0058
Rye 15 A	103	4.1	0.6	0	33.9	57.3	30	5.3	0.25	0.020	0.032	0.22		0.15	-	0.048	-	0.086	†
Lima bean 16 B	103	-	0.6	0	29.0	55.3	35	5.7	0.28	0.0042	0.050	0.18		0.17	-	0.035	-	0.018	-
Peas 17	103	-	0.6	0	32.8	54.6	29	5.0	0.24	0.0072	0.029	0.19		0.15	-	0.049	-	0.0055	0.00083
Soy 18	103	1.3	0.6	0	30.0	46.0	34	4.7	0.14	0.030	0.038	0.23		0.073	-	0.10	-	0.045	0.018
Rice 19 B	103	73.7	0.6	0	29.8	49.6	30	5.2	0.32	0.011	0.033	0.29		0.21	-	0.055	-	0.043	-
Corn 20 A	103	2.5	0.6	0	31.8	49.1	30	5.4	0.26	0.011	0.032	0.29		0.16	-	0.066	-	0.0032	0.0064

*Values from the literature were compiled from data given in references 49 to 56 inclusive.
†Amino acids were compiled from data given in references 34 to 48 inclusive.

a week or so, so that its effects will not become cumulative." One of us (L. Z. W.), in treating eczematous infants with the included milk substitutes, in practically all cases alternated the dietary every other day between two formulas given the infant at the beginning of his treatment. This was done because early in the study, frequent acquisition of sensitivity to the feeding was noted. With the alternation not only of the milk substitute but also of all the articles of diet, the frequency of such sensitization was markedly diminished.

Surface tension, curd tension, and pH of the formulas were found experimentally by one of us (P. C. S.). Values such as protein, fat, carbohydrate, calcium, phosphorus, iron, copper, amino acid, fiber, ash, iodine, iodine number, and acid number were calculated from data given in the literature, average values being taken in as many cases as possible.[31-53] This is reasonably justifiable when it is considered that cereals vary in composition both as to season and locality. Surface tension was found by means of a Du Nuoy tensiometer by the conventional method. Curd tension was obtained by means of the Hill curd tension method as issued by the American Dairy Science Association report of June, 1941. The pH was obtained by a Beckman pH instrument, using glass electrodes. Amino acid data were found to be scanty. However, it was possible to determine most of the indispensable amino acids as defined by Rose,[54] who offers the following table:

INDISPENSABLE AMINO ACIDS	DISPENSABLE AMINO ACIDS
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Marleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Hydroxyglutamic acid
Methionine	Citrulline
Valine	Tyrosine
Arginine	Cystine (may supplement a limited supply of methionine)

SUMMARY OF CASES

CASE 1.—Female infant had severe colic and beginning eczema within the first week of life. Both evaporated cow's milk and evaporated goat's milk were tolerated so poorly that diarrhea and vomiting also ensued. All nine substitutes were used without complete relief of the eczema but with complete relief of the colic, diarrhea, and vomiting. The infant was hospitalized for a period of three days for control. Oat and barley substitutes are now being alternated with sesame oil fortification. The eczema is approximately 75 per cent clear. The course of this infant has been one of the stormiest of the entire series. Clinical relief at time of writing has not yet been attained.

CASE 2.—Male infant had upper respiratory infection at 6 months of age, followed within ten days by eczema. Both evaporated cow's milk and evaporated goat's

milk were not tolerated. Substitutes were begun at 9½ months with almost immediate relief. Since onset of treatment there have been three upper respiratory infections with transient exacerbations of eczema.

CASE 3.—Female infant had severe colic and diarrhea beginning at 6 weeks of age which did not respond to either cow's or goat's evaporated milk. Substitutes were begun at one month, twenty-eight days with relief within three days. Eczema began at 3 months of age and soy, which was then being used, was discontinued, again with almost immediate relief. The oil was changed from cottonseed to olive and finally to sesame because of loose stools.

CASE 4.—Male infant had eczema which began at 2 months, 9 days of age while on cow's evaporated milk with cane sugar. Goat's milk was not attempted because of economic reasons. Substitutes were begun at the age of 2 months, 9 days, with relief in a few days.

CASE 5.—Male child, 22 months old, was first seen in consultation during an attack of bronchopneumonia. Eczema had first appeared at the age of 3 weeks and asthma of persistent character at 1 year. Substitutes were offered with relief of both asthma and eczema. This child had been under constant treatment with various dietary eliminations, in the hands of several doctors, with no relief. Both evaporated cow's and goat's milk had been attempted without success.

CASE 6.—Male child was seen at 19 months of age. Various types of local therapy and dietary eliminations had not altered a flexural eczema which had been present for seven months. Cow's and goat's evaporated milk were attempted with no relief. Substitutes were begun at the age of 20 months, 27 days, with clearing of the rash within a short time. This child has had two upper respiratory infections and Roseola Infantum since without return of the eczema.

CASE 7.—Male infant, son of one of us (P. C. S.), had upper respiratory infections at 1 month, 6 days of age and again at 10½ weeks. Seborrheic crusting of the scalp and facial atopic changes began at 2½ months, while on evaporated cow's milk and cane sugar. Substitutes were begun at 3 months with relief within twelve days. Evaporated cow's milk was again attempted at 7 months. When 1½ teaspoons had been reached as the daily ration, eczema returned. Elimination of the milk again cleared the skin within a few days.

CASE 8.—Female infant had eczema which appeared first in flexure of right elbow and rapidly spread despite the use of both cow's and goat's evaporated milk. Soy substitute was begun at 7 months, 4 days of age, with rapid recovery.

CASE 9.—This infant had a very emphasized allergic familial history. An upper respiratory infection at the age of 3 months, and a stomatitis at 4½ months were followed by eczema which persisted until substitutes were begun at 5½ months. Two upper respiratory infections have occurred since the beginning of treatment with no evidence of recurrent rash.

CASE 10.—Severe colic, vomiting, and diarrhea from birth to 3 weeks of age, not relieved by cow's or goat's evaporated milk, responded rapidly to soy substitute. Succeeding an upper respiratory infection at 1 month, the stools again became loose and colic returned. Several changes with temporary relief after each alternation were followed by an exacerbation of the upper respiratory infection. Within eight

days, this infant developed startling pallor and was hospitalized. On first day of hospital stay, the blood count was reported: hemoglobin, 61 per cent; red blood cells, 2,480,000; white blood cells, 7,300; segmented leucocytes, 43; stabs, 3; lymphocytes, 50.5; monocytes, 3.5. The red blood cells showed marked anisocytosis and poikilocytosis; moderate polychromasia; no nucleated red blood cells found. Small transfusions of citrated blood of 75 c.c., 60 c.c., and 65 c.c., respectively, were given on the next three days. A repeat count three days after the first demonstrated the following change: hemoglobin, 68 per cent; red blood cells, 3,700,000; white blood cells, 8,700; segmented leucocytes, 54; stabs, 11.5; lymphocytes, 26; monocytes, 8.5. The red cells showed a moderate degree of anisocytosis and poikilocytosis. Despite high vitamin and iron therapy and an alternation of substitutes to relieve the constantly loose stools, a fairly hectic course was described for four weeks. A course of liver concentrate intramuscularly was offered which finally did improve the hemogram to: hemoglobin, 78 per cent; red blood cells, 4,330,000; white blood cells, 6,300; segmented leucocytes, 35; stabs, 3.5; lymphocytes, 52.5; eosinophiles, 1.0; basophiles, 0.5; monocytes, 7.5. Even after discharge, stools remained loose. Since the entire list of substitutes had been attempted without much effect, protein milk was begun, a few drops daily. Severe colic and profuse diarrhea began after three days, which was relieved when the protein milk was withdrawn. Since this episode this infant's progress has been singularly good and the stools normal.

CASE 11.—Male child with history of eczema over face and thighs for a three-month period, unrelieved by cow's and goat's evaporated milk. Rash cleared nine days after beginning substitutes.

CASE 12.—An upper respiratory infection at 4 months of age was succeeded by constant nasal stuffiness and asthma. Soy substitute was begun at seven months with relief within a week. Another upper respiratory infection was experienced two weeks later which subsided without incident.

CASE 13.—Cradle cap at 5½ weeks of age which subsided with local therapy and cow's evaporated milk fortified with cane sugar. Facial atopic dermatitis began at 3 months of age. Substitutes were begun one month later and rapid change ensued. Another upper respiratory infection with transient flare of eczema occurred three weeks later.

CASE 14.—Typical atopic dermatitis of one year's duration cleared within five weeks with substitute therapy. Previously evaporated cow's and goat's milk were attempted without relief.

CASE 15.—This infant experienced a thrush infection at two weeks, an upper respiratory infection at four and one-half weeks, and an ammoniacal type of dermatitis which became eczematoid and spread to face and body flexures. Cow's and goat's evaporated milk were attempted. Taro substitute cleared the rash rapidly and changed the stools from a loose characteristic to normal. Shortly after relief, an upper respiratory infection, which developed into a pneumonia, occurred without any recurrent eczema. Taro substitute was changed to less costly substitutes more recently. Another upper respiratory infection at 9 months, 10 days occurred without further incident.

CASE 16.—Female infant, breast-fed, was seen at the age of 2½ months, with typical atopic dermatitis. Elimination diets for the mother were followed by some

TABLE IV

TABULATION OF CASES

PART I

NO.	COMPLAINT	SEX	FLOUR		OIL		BIRTH				BEGINNING OF COMPLAINT					BEGINNING OF ℞ WITH SUBSTITUTES				
			NUMBER OF TYPES USED	FLOUR LAST USED	NUMBER OF TYPES USED	OIL LAST USED	DATE	WEIGHT		LENGTH (INCHES)	AGE		WEIGHT		LENGTH (INCHES)	AGE		WEIGHT		LENGTH (INCHES)
								LBS.	OZ.		MO.	DAYS	LBS.	OZ.		MO.	DAYS	LBS.	OZ.	
1	E.	F.	9	Oat and barley	3	Sesame	8/28/41	6	14	20½	1	8	9	7½	21	2	6	11	6	22½
2	E.	M.	3	Oat and barley	1	Cottonseed	3/26/41	7	4	21	6	10	17	11¼	26	9	14	21	2	28
3	G. I.	F.	3	Oat and barley	3	Sesame	11/ 2/41	6	8½	19½	1	14	8	11¾	20¾	1	28	9	12¾	21½
4	E.	M.	2	Soy and barley	1	Sesame	1/18/42	7	12	21⅛	2	6	12	8	23⅜	2	9	12	8	23⅜
5	E. and A.	M.	1	Soy	1	Sesame	4/15/40	8	13	-	O A=12	E=3 0	-	-	-	22	7	-	-	-
6	E.	M.	2	Soy and barley	1	Cottonseed	1/28/40	8	11	21	12	0	-	-	-	20	27	30	3	34¼
7	E.	M.	4	Soy and barley	2	Olive	8/23/41	6	4	21	2	14	12	½	23¼	3	0	13	1¼	23½
8	E.	F.	2	Soy and barley	2	Sesame	6/23/41	3	1	-	6	21	13	14¼	23¼	7	4	14	10½	24
9	E.	M.	4	Soy and barley	1	Cottonseed	6/ 2/41	6	11½	19¼	4	25	15	5	25	5	2	15	6½	25
10*	G. I.	F.	8	Soy	3	Sesame	11/21/41	7	3	19½	Birth		7	3	19½	0	21	7	8	20¼
11	E.	M.	2	Soy	1	Olive	9/ 1/40	6	9	19	14	0	-	-	-	17	0	-	-	-
12	A.	M.	2	Soy and barley	1	Olive	7/ 2/41	8	7	21¾	4	0	17	2½	27¾	7	0	21	1	30¼

TABLE

PART

NO.	CLINICAL RELIEF†					LAST EXAMINATION					
	AGE		WEIGHT		LENGTH (INCHES)	DATE	AGE		WEIGHT		LENGTH (INCHES)
	MO.	DAYS	LBS.	OZ.			MO.	DAYS	LBS.	OZ.	
1	-	-	-	-	-	4/14/42	7½	0	17	11½	26¼
2	10	21	20	4	28	4/14/42	12	19	22	8	29½
3	2	1	9	12¾	21½	4/14/42	5	12	13	14	25
4	2	14	13	1½	24	4/16/42	3	0	14	0	24¼
5	22	17	-	-	-	4/11/42	24	0	29	11	36
6	21	7	28	12	33	4/16/42	26	14	31	7	35
7	3	12	13	0	23½	3/26/42	7	3	17	12	27¼
8	7½	0	14	4¾	24⅛	3/20/42	8	25	15	0	25
9	5½	0	15	4	25	3/17/42	9½	0	20	9	27½
10	1	0	7	13½	20½	4/ 9/42	4	19	12	½	23½
11	17	10	21	13½	31	2/ 9/42	17	10	21	13½	31
12	7	7	20	13½	30¼	4/ 3/42	9	0	22	9½	31

improvement but not complete relief. Sensitivities to milk and egg in the mother's diet were definitely established by exacerbations in the eczema whenever these foods were resumed in the dietary. Substitutes gave rapid relief. Upper respiratory infections were experienced at 4½ months and 5½ months without recurrence of the rash.

CASE 17.—Atopic dermatitis at 1 month of age with no relief with cow's evaporated milk. Some improvement ensued with alternation of substitute with evaporated goat's milk. The rash cleared only after withdrawal of goat's milk. Two slight exacerbations with other foods have occurred which subsided upon the removal of the offenders from the diet.

CASE 18.—This child was seen at 5¾ months with severe seborrheic crusting of the scalp and facial eczema. The only substitutes in the entire series which were tolerated were oat and barley. This child has demonstrated multiple sensitivities and has had numerous exacerbations of rash which were relieved by removing offending foods.

CASE 19.—Eczema began at 1 month of age which responded nicely to cow's evaporated milk. Reappeared at eight months, twelve days, and disappeared only after institution of substitute therapy.

CASE 20.—An upper respiratory infection ending in otitis media was soon followed by the appearance of eczema. Substitute therapy afforded rapid relief.

IV—CONT'D

I—CONT'D

DEVELOPMENTAL SUMMARY												COMPLICATIONS DURING TREATMENT
BIRTH TO ONSET OF COMPLAINT			ONSET OF COMPLAINT TO BEGINNING OF R			BEGINNING OF R TO CLINICAL RELIEF			CLINICAL RELIEF TO LAST EXAMINATION			
WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	
LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	
2	9½	½	1	14½	1½	–	–	–	–	–	–	Colic diarrhea; secondary infection of skin; two U. R. I.
10	7¼	5	3	6¾	2	0	-14	0	2	4	1½	U. R. I.
2	3¼	1¼	1	1	¾	0	0	0	4	1¼	3½	Slight E.
4	12	2¼	0	0	0	0	9½	⅝	0	14½	¼	None
–	–	–	–	–	–	–	–	–	–	–	–	Bpn.
–	–	–	–	–	–	-1	- 7	-1¼	2	11	2	U. R. I.
5	12½	2¼	1	¾	¼	0	- 1¼	0	4	12	3¾	U. R. I.
10	13¼	–	0	12¼	¾	0	- 5¾	⅛	0	11¼	⅞	U. R. I.
8	9½	5¾	0	1½	0	0	- 2½	0	5	5	2½	Stomatitis; three U. R. I.
0	0	0	0	5	¾	0	5½	¼	4	3	3	U. R. I. Secondary anemia
–	–	–	–	–	–	–	–	–	–	–	–	None
8	11½	6	3	14½	2½	0	- 3½	0	1	12	¾	U. R. I.

COMMENT

1. In our opinion, the chief value of the preceding investigation lies not in the nine milk substitutes here offered but in the possibility of constructing an infinite number of substitutes from cereals or vegetables indigenous to any locality after determining their chemical analysis.

2. During times of war and possible diminution in available dairy supplies, the ability to prepare from local sources, everywhere, a complete substitute for milk, is a distinct and timely advantage which cannot be overemphasized.

3. With few exceptions, before placing any patient on milk substitutes during this investigation, whole milk boiled for ninety minutes, evaporated cow's milk, and finally evaporated goat's milk were employed, until, finally, no other course was open but to remove all milk. Similarly, the carbohydrate was changed to cane sugar and finally to dextrose.

4. These substitutes have been in use both in an eczema ward under the direction of one of us (L. Z. W.) and in the outpatient clinic at the Los Angeles County Hospital since Jan. 1 of this year. Within the next four months the results of this investigation will be offered.

5. The developmental progress of the patients included attest to the satisfaction of their metabolic needs.

6. The palatability of the formulas aids in the ease of treatment through an age period which frequently offers poor cooperation.

7. Table IV offers in its Developmental Summary a review of weight and length gain in the following four periods: birth to onset of complaint; onset of complaint to beginning of treatment; beginning of treatment to clinical relief; clinical relief to last examination.

8. More than 50 per cent of the eczemas herein recorded occurred after a period of infection.

9. During the course of treatment, 85 per cent of the infants reported experienced some infection.

10. While undergoing treatment, six patients suffered a minimum loss of weight. All patients described substantial gains in both weight and height from the period of clinical relief to the last examination, except one who lost one-half ounce.

11. Two patients required hospitalization; one because of a severe anemia which developed within one week after a pharyngitis and the second for a period of two or three days for control of the eczema.

12. Of the patients listed, 20 per cent had some slight to moderate exacerbation of eczema during an upper respiratory infection or a teething episode even after clinical relief. These episodes were short lived.

13. One patient of the series offered still retains some definite facial eczema which, however, is clearing rapidly.

14. Of interest is the fact that oat and barley flours, and olive and sesame oils were most frequently tolerated.

15. The usual difficulties in the treatment of eczemas will still hold. There will still be numerous failures in attaining desired results. These milk substitutes are offered only as balanced foods to take the place of milk when milk cannot be tolerated. Further, the wide choice of substitutes afforded makes the task of the doctor a little easier and certainly more satisfying.

SUMMARY

In eczema, especially infantile eczema, milk allergy plays a major role. The majority of eczematous infants react to the curd of milk whether there is sensitivity to the casein alone or sensitivity to both casein and lactalbumin. Casein of both cow's milk and goat's milk is almost identical immunologically. Because of the greater proportion of casein in cow's milk than in human milk, there is a greater chance of casein sensitization.

Soybean flour varies widely in protein, fat, and phosphorus content. Therefore, to avoid variations in soy formulas, processing of the flour must be investigated thoroughly before using as the base for "soy milk." The literature has demonstrated the necessity of the addition of both calcium and phosphorus to milk substitutes rather than calcium alone.

TABLE IV—CONT'D

PART II

NO.	COM-PLAINT	SEX	FLOUR		OIL		BIRTH				BEGINNING OF COMPLAINT					BEGINNING OF ℞ WITH SUBSTITUTES				
			NUM-BER OF TYPES USED	FLOUR LAST USED	NUM-BER OF TYPES USED	OIL LAST USED	DATE	WEIGHT		LENGTH (INCHES)	AGE		WEIGHT		LENGTH (INCHES)	AGE		WEIGHT		LENGTH (INCHES)
								LBS.	OZ.		MO.	DAYS	LBS.	OZ.		MO.	DAYS	LBS.	OZ.	
13	E.	F.	2	Soy and barley	1	Cotton-seed	10/ 6/41	7	5	20	3	21	15	0	24½	4	0	16	0	24¾
14	E.	M.	2	Soy and oat	1	Sesame	1/ 2/41	7	7	-	4	14	13	10	-	14	18	22½	0	29
15	E. G. I.	F.	4	Soy and barley	1	Cotton-seed	5/ 6/41	6	12	19	3½		13	7¾	24¾	6	0	15	14	26½
16	E.	F.	3	Soy, barley, and oat	1	Cotton-seed	8/22/41	8	2	20¼	1	21	-	-	-	3	21	14	5½	25
17	E.	M.	2	Soy and barley	2	Sesame	11/ 4/41	8	8½	21⅛	1	0	9	12¾	21½	1	11	10	14	22¼
18	E.	M.	9	Oat and barley	3	Sesame	5/17/41	7	5	20	3	21	-	-	-	6	0	19	3	26¾
19	E.	M.	3	Oat and barley	3	Sesame	5/11/41	10	7	22¾	8	4	-	-	-	8	12	22	4¼	29
20	E.	M.	2	Oat and barley	1	Cotton-seed	5/18/41	7	10	20	6	27	21	5¾	27	7	21	22	9½	28

TABLE
PART

NO.	CLINICAL RELIEF					LAST EXAMINATION					
	AGE		WEIGHT		LENGTH (INCHES)	DATE	AGE		WEIGHT		LENGTH (INCHES)
	MO.	DAYS	LBS.	OZ.			MO.	DAYS	LBS.	OZ.	
13	4	9	16	0	24¾	3/31/42	5	25	18	0	25¾
14	15	10	–	–	–	4/13/42	15	11	–	–	–
15	6	25	15	7¾	26½	4/11/42	11	0	20	13	28¾
16	4	0	15	2	25¼	2/27/42	6	5	16	14	26¾
17	1	25	11	14¼	22¾	4/11/42	5	7	17	11½	25½
18	6	21	19	5½	27	3/23/42	10	7	21	8	28½
19	9	0	22	14	29	3/ 8/42	10	25	22	13½	30
20	8½	0	22	11½	28¼	4/15/42	11	0	23	12½	28¾

*Fluctuating course, *see* summary of cases.
†Slight to moderate erythemia only.
E. = Eczema.
G. I. = Gastrointestino allergy (vomiting, colic, diarrhea).
A. = Asthma.
U. R. I. = Upper respiratory infection.
Bpn. = Bronchopneumonia.

Nine milk substitutes made from oat, barley, soy, lima bean, pea, taro, rice, rye, and corn flours have been constructed with the addition of oil (cottonseed, olive, sesame, corn, peanut, and soy) and gelatin, dextrose, imitation vanilla, salt, crushed bone phosphate or dicalcium phosphate, 10 per cent aqueous solution of ferric chloride, and in several, saccharin. Correct chemical constitution of these substitutes has been satisfied according to the available evidence in the literature of the past fifteen years. Ten milligrams of iron, 1 Gm. of calcium, and 1.3 Gm. of phosphorus, with a calcium-phosphorus ratio somewhere between 1:1 and 2:1, have been taken as the daily minimum intake. The amounts of these substances have been added in correct balance in all the substitutes listed. Protein percentage in the diluted formulas varies from 2.7 to 3.4 per cent; fat, from 3 to 3.9 per cent; carbohydrate, from 8.3 to 11.0 per cent. By clinical experience and comparison with successful available milk products, these ranges have appeared desirable. This must be modified by the thought that, because these are home preparations, the percentage of any of these constituents may be varied according to the specific idiosynerasy of the individual patient. This constitutes an advantage which cannot be matched in existing commercial formulas already constituted in certain definite proportions, unchangeable, except through dilution. The caloric value of one quart of the substitutes offered, according to the flour employed, varies from 700 to 900 calories, substantially greater than equivalent amounts of milk and

TABLE IV—CONT'D

PART II

DEVELOPMENTAL SUMMARY												COMPLICATIONS DURING TREATMENT
BIRTH TO ONSET OF COMPLAINT			ONSET OF COMPLAINT TO BEGINNING OF R			BEGINNING OF R TO CLINICAL RELIEF			CLINICAL RELIEF TO LAST EXAMINATION			
WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	WEIGHT GAIN		LENGTH GAIN	
LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	LBS.	OZ.	(INCHES)	
7	11	4½	1	0	¼	0	0	0	2	0	1	U. R. I.
6	3	–	8	14	–	–	–	–	–	–	–	None
6	11¾	5¾	2	6¼	1¾	0	6¼	0	5	5¼	2¼	Virus pneumonia; U. R. I.
–	–	–	–	–	–	0	12½	¼	1	12	1½	U. R. I.
1	4¼	⅜	1	1¼	¾	1	¼	½	5	13¼	2¾	None
–	–	–	–	–	–	0	2½	¼	2	2½	1½	Three U. R. I.
–	–	–	–	–	–	0	9¾	0	0	-½	1	None
13	11¾	7	0	3¾	1	0	2	¼	1	1	½	Two U. R. I.

equal to or greater than equivalent amounts of calculated formulas made with milk and added carbohydrate. Gelatin as a *complementary* protein fortification rather than as a sole source of protein seems adequate. The increased absorptive ratio of vegetable oils over butter fat makes such fortification desirable.

Correct physical constitution of the substitutes with surface tension approximating that of milk, curd tension that of a soft curd milk, and pH about the neutral point has been attained. These substitutes combine the advantages of a soft curd milk with the advantages of an acidified milk.

The palatability, fluidity, low cost, ease of availability, and ease of preparation are all exemplified in the comparative lack of difficulty with which these preparations have been offered to both the patient and the one preparing the formula.

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THE BLOOD LEVEL OF VITAMIN B_1 IN HEALTHY CHILDREN AND ITS RELATION TO THE URINARY THIAMINE

REUEL A. BENSON, M.D., C. MICHAEL WITZBERGER, M.D., LAWRENCE B. SLOBODY, M.D., AND LIESE LEWIS, PH.D.
NEW YORK, N. Y.

THERE have been few reports on the blood level of vitamin B_1 in healthy children. Urinary thiamine excretions have been studied extensively and have been found to reflect the degree of thiamine tissue saturation of the body. It seemed to us profitable to study the relationship of the blood B_1 to the urinary thiamine excretion.

Thiamine is found mainly as thiamine pyrophosphate, that is, cocarboxylase, in the blood and tissues. It is as this coenzyme that vitamin B_1 functions in the metabolism of carbohydrates. This active form of thiamine, cocarboxylase, exists in the cellular elements of the blood, and only about 10 per cent of the total blood vitamin B_1 content is present in the plasma as free thiamine. Thus, blood determinations of total vitamin B_1 (cocarboxylase plus free thiamine), must be done on whole blood rather than on plasma.

Three principal methods have been used for determining vitamin B_1 in the blood. The first is based on an observation by Ochoa and Peters,[1] that the amount of carbon dioxide evolved from pyruvic acid in the presence of washed yeast and maximal amounts of thiamine will be directly proportional to the amount of cocarboxylase which is added to the system. The second method is dependent on the fact that vitamin B_1 stimulates the growth of the fungus *Phycomyces blakesleeanus*.[2, 3] In the third method the cocarboxylase is split to free thiamine and this plus the preformed thiamine is converted to thiochrome. The fluorescence of the thiochrome is then quantitatively measured.[4]

Results of blood determinations in normal individuals as reported by other observers are found in Table I. Two of these studies use children as subjects. Wortis, Goodhart, and Bueding[5] determined the cocarboxylase content of the blood in fifty children from 4 to 15 years of age, none of whom exhibited any of the generally recognized clinical signs of vitamin B_1 deficiency in children. These children had a range of 4 to 13 μg with a mean of 7.5 (plus or minus 1.82) μg per 100 c.c. Schlutz and Knott[6] do not give any average for their healthy children but believe that an infant or young child should have a value of cocarboxylase in the blood of 10 μg or more per 100 c.c. of blood.

From the Frederick S. Wheeler Research Laboratory and the Pediatric Department of the New York Medical College.

TABLE I

AMOUNT OF VITAMIN B_1 IN NORMAL HUMAN BLOOD

METHOD	AUTHOR	RANGE IN μG (PER CENT)	MEAN IN μG (PER CENT)
Cocarboxylase	Wortis, Goodhart, and Bueding[5]	4 to 13 (Children)	7.5 ± 1.82
Cocarboxylase	Goodhart and Sinclair[9]	4.5 to 12	7.0 ± 2.1
Cocarboxylase	Schlutz and Knott[6]	Children	10.0
Phycomyces	Rowlands and Wilkinson[10]	6.5 to 16.5	
Phycomyces	Lehman and Nielsen[11]	7 to 13	9 (Average)
Phycomyces	Sinclair[3]	5.5 to 12.5	7.4 ± 1.4
Thiochrome	Widenbauer, Huhn, and Disselhoff[12]	2.0 to 11.0	7.0 (Average)
Thiochrome	Ritsert[13, 14]	3.0 to 15.0	

PLAN OF STUDY

There were two main problems in planning this study. First, the selected children, in addition to being clinically healthy, had to be known to have thiamine tissue saturation. Second, the method for the blood determination had to be accurate and reasonably easy to perform routinely.

The children used in this study were hospitalized and so could be controlled and carefully observed. A complete history was taken, and physical and routine laboratory examinations were done to determine whether the child was clinically healthy. Furthermore the urinary thiamine excretion in relation to the dietary thiamine intake was estimated for each child to ascertain thiamine tissue saturation. We[7, 8] have reported that a child with thiamine tissue saturation will excrete more than 20 per cent of an adequate dietary thiamine intake. For example, if such a child ingests 1,000 μg of thiamine in the diet, at least 200 μg will be excreted in the urine. Thus the selected children were known to be clinically healthy and to have excreted 20 per cent of their dietary intake; that is, their tissues were thiamine saturated.

Each child was permitted to eat what and as much as he wished from the hospital dietary. The daily dietary intakes of carbohydrates, proteins, fats, total calories, and thiamine were computed. The daily urinary thiamine excretion was measured during an entire week by a thiochrome method. During this week each child had four pre-breakfast blood determinations for vitamin B_1.

We have used a modified thiochrome method for the blood determinations. Hennessy and one of us (L. L.) will report on this method in detail.[15] This method determines the total vitamin B_1 content of the blood; that is, the cocarboxylase plus the free thiamine.

Five cubic centimeters of blood are added to 20 c.c. of 1 per cent acetic acid. After heating in boiling water for ten minutes, the pH is adjusted to 4.8 to 5.0. Vitamin B_1 free taka diastase is added and the blood incubated for one and one-half hours at 45 to 50° C., in order to convert the cocarboxylase to free thiamine. It is then made up to volume, centrifuged, and 40 c.c. of the supernatant is removed and used for the base exchange. This consists in passing the fluid through

a column of Decalso, washing with water, and eluting with acid potassium chloride. Ten cubic centimeters of the eluate are oxidized to thiochrome. The thiochrome fluorescence is then quantitatively measured in the fluorophotometer.

RESULTS

The individual results for forty-five children will be found in Table II. The children ranged in age from 4 to 12 years. There were twenty-two boys and twenty-three girls. The lowest caloric intake was 1,624,

TABLE II

CASE NO.	SEX	AGE (YR.)	WT. (POUNDS)	AVERAGE CALORIC INTAKE	AVERAGE B_1 INTAKE	URINE		BLOOD			
						AVERAGE B_1 OUTPUT	B_1 OUTPUT / B_1 INTAKE (PER CENT)	LOW	HIGH	AVERAGE	NUMBER OF DETERMINATIONS
1	M.	7	50	2,232	882	179	20	7.8	10.8	9.3	4
2	M.	9	57	2,149	936	186	20	6.8	8.4	7.7	4
3	F.	5½	41	1,667	669	137	21	8.4	11.5	9.5	3
4	F.	8	70	2,069	876	184	21	7.6	9.7	8.6	4
5	F.	9	93	2,182	885	185	21	4.8	7.4	6.5	4
6	M.	10	77	3,051	1,173	246	21	5.3	8.1	6.6	4
7	F.	12	72	2,372	915	195	21	5.6	7.3	6.4	4
8	F.	8	77	2,177	894	200	22	7.9	8.9	8.4	4
9	F.	7	48	1,964	816	189	23	7.5	8.7	8.2	4
10	F.	8	53	2,109	843	198	23	6.3	8.5	7.2	4
11	M.	7	59	1,940	903	213	24	7.8	9.8	8.4	4
12	M.	9	70	1,739	687	165	24	6.1	7.0	6.9	4
13	M.	9	72	1,804	678	164	24	6.7	9.3	8.3	4
14	M.	11	98	1,713	648	154	24	7.0	8.5	8.0	4
15	F.	6	48	2,119	891	226	25	6.4	8.9	7.7	4
16	F.	7	47	2,047	846	210	25	6.5	8.5	7.3	4
17	F.	10	61	1,677	630	160	25	7.2	10.6	8.4	4
18	F.	11	66	2,174	951	234	25	6.8	7.5	7.1	4
19	M.	11	91	2,357	855	213	25	6.7	8.1	7.6	4
20	M.	5	40	1,951	771	205	27	7.6	12.3	9.6	4
21	F.	8	74	2,113	762	208	27	7.0	8.7	7.7	4
22	M.	8	62	2,201	903	243	27	8.3	10.1	8.9	4
23	M.	11	64	1,963	822	237	29	6.6	10.9	8.9	4
24	F.	9	71	2,075	834	251	30	5.4	7.5	6.6	4
25	M.	11	80	1,826	750	225	30	6.3	6.8	6.6	4
26	M.	4	35	2,004	801	249	31	8.1	10.7	9.4	4
27	F.	5	41	1,881	765	235	31	7.2	9.6	8.2	4
28	M.	5	46	2,059	909	294	32	6.7	8.6	7.2	4
29	F.	8	56	2,043	828	270	32	6.3	7.7	6.9	4
30	F.	9	53	1,789	735	233	32	9.3	10.4	9.9	4
31	F.	10	79	2,228	921	291	32	6.7	7.5	7.0	3
32	M.	10	76	1,649	657	207	32	6.2	7.2	6.6	4
33	F.	11	79	2,365	855	269	32	5.9	7.5	6.4	4
34	F.	10	100	1,797	741	244	33	5.8	8.6	7.6	4
35	M.	10	64	2,037	696	237	34	7.6	9.8	9.0	5
36	M.	9½	61	1,624	684	242	35	7.0	9.4	7.9	4
37	M.	11	53	1,634	633	219	35	7.0	8.6	7.7	4
38	F.	11	80	2,126	879	318	36	6.4	6.6	6.5	3
39	M.	11	69½	1,731	705	253	36	6.0	8.4	7.5	4
40	M.	10	80	1,787	630	241	38	6.8	8.4	7.2	4
41	F.	9	77	2,177	852	334	40	5.9	8.2	7.2	4
42	M.	12	85	2,449	1,008	404	40	6.5	8.2	7.3	4
43	F.	6	50	2,409	894	363	41	7.9	8.6	7.8	4
44	F.	6	50	2,212	864	360	42	7.2	7.8	7.5	4
45	M.	10	63	1,859	768	345	45	7.2	9.5	8.1	4

the highest 3,051. The dietary thiamine intake ranged from 630 to 1,170 μg. The lowest urinary thiamine excretion was 137 μg, the highest was 404 μg. No child excreted less than 20 per cent of the dietary thiamine intake.

A total of 177 blood determinations for vitamin B_1 were done and are visualized on the scattergram (Fig. 1). Each child had four blood determinations. The lowest single determination of the blood level of vitamin B_1 was 4.8 μg per 100 c.c., the highest was 12.3. However, the lowest average blood level of B_1 was in Cases 7 and 33, with 6.4 μg per 100 c.c. The highest was in Case 30 with 9.9 μg. The mean vitamin B_1 level for all the children was 7.8 (plus or minus 1.3) μg per 100 c.c.

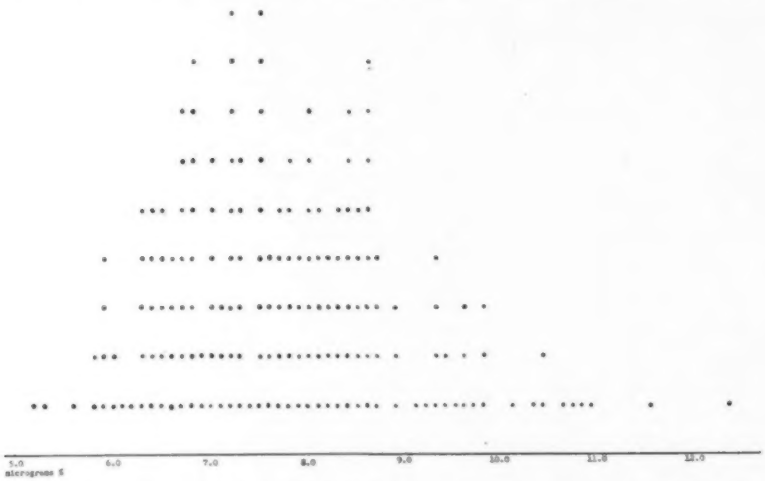

Fig. 1.—Scattergram of 176 blood B_1 determinations in normal children.

COMMENT

The daily variations in blood vitamin B_1 in an individual child did not follow the daily urinary thiamine output. In Fig. 2 the daily relationships between blood vitamin B_1 and urinary thiamine output of the patient in Case 42 is graphically presented. It will be noted that although the daily urinary thiamine varied from 287 to 625 μg, the daily blood levels did not change accordingly.

The blood level of vitamin B_1 was not proportional to the amount of thiamine excreted or to the percentage of the dietary thiamine which was excreted in the urine. For example, the patient in Case 42 excreted 404 μg of thiamine in the urine, which was 40 per cent of the dietary thiamine, and had an average blood level of 7.3 μg per 100 c.c. The patient in Case 3 excreted 137 μg in the urine, which was 21 per cent of the thiamine in the diet, and had an average blood level of 9.5 μg per 100 c.c. This may speak for an individual fixed blood concentration in

thiamine-saturated individuals which cannot be raised. If additional thiamine is given, the urinary thiamine excretion increases, but it is possible that the blood level is not raised. At present we are working on this point.

The range of the blood level for any particular child was narrow. The widest range was found in Case 20, 7.6 to 12.3 μg. Most of the children varied less than 2 μg between their lowest and highest blood levels. Although the lowest single determination was 4.8 μg, the lowest average for any particular child was 6.4 μg.

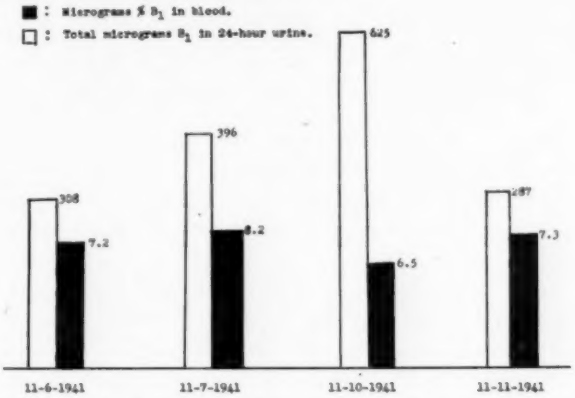

Fig. 2 (Case 42).—Individual daily variations of blood B_1 in relation to urinary B_1.

The blood levels in children seem to approximate those in adults. This is not surprising if one remembers that the entire blood chemistry of the child is not significantly different from the adult. We have obtained blood levels of vitamin B_1 in newborn infants and thus far have found them to be comparable to those of older children. In fact, the average blood level in newborn infants seems to be higher than in children.

Our range of 4.8 to 12.3 μg with a mean of 7.8 ± 1.3 compares rather closely with that of Wortis, Goodhart, and Bueding.[5] This may mean that the groups of children selected by them and by us had tissue saturation with thiamine. However, it is possible that the blood levels do not fall in the face of mild or moderate degrees of tissue unsaturation. Then the blood level of vitamin B_1 would be useless for diagnosing subclinical deficiency; that is, thiamine tissue unsaturation without clinical signs and symptoms. We are now collecting data on this phase.

SUMMARY AND CONCLUSIONS

1. In 177 determinations on forty-five healthy children, the blood level of vitamin B_1 ranged from 4.8 to 12.3 μg with a mean of 7.8 ± 1.3 μg.

2. The daily variations in blood vitamin B_1 in an individual child did not follow the daily urinary thiamine outputs.

3. The height of the vitamin B_1 blood level had no relationship to the amount of thiamine excreted or to the percentage of dietary thiamine excreted in the urine.

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OBSERVATIONS ON SCHICK TEST REACTIONS AND SERUM ANTITOXIN TITERS AFTER INJECTIONS OF TOXOID

BEN BENJAMIN, M.D., GRANT FLEMING, M.D., D.P.H., MONTREAL, CAN., AND MARY A. ROSS, PH.D., TORONTO, CAN.

THE results of a survey to determine the status of diphtheria immunity as gauged by Schick tests in a group of children who had received injections of toxoid a number of years previously have been reported in a former communication.[1] During the course of this study it seemed of interest and importance to measure quantitatively the amounts of serum antitoxin which some of these children possessed, particularly those whose reactions to the test might be interpreted as doubtful, as well as those who reverted to positive after having had negative reactions to previous tests or became negative after previously reacting positively without having received any further toxoid.

All the Schick tests were performed on the anterior surface of the forearm by the intradermal injection of 0.1 c.c. of a dilution of diphtheria toxin conforming to standard requirements for combining power and toxicity.[2] A control, using 0.1 c.c. of 1:100 diluted toxoid, was done on the other forearm with each test. All the tests and controls were read and recorded on the fifth day after they were administered. When the result was not unquestionably positive or negative, it was listed with a "?." The latter included a very slight reaction (less than 5 mm. in the greatest diameter) to toxin accompanied by a negative control. A few showed a very slight reaction to toxin and a very slight reaction to the control. When the test produced an area of faint erythema (5 mm. or more in the greatest diameter) and the control was negative, the result was listed as slightly positive. This was done to observe if sera from children who showed such reactions contained more antitoxin than those from others whose reactions were more strongly positive.

Most of the blood specimens were drawn on the fifth day after the tests, when they were read; in a few instances, nine and seventeen days after the tests were performed; and in a small number, immediately before the administration of the tests, as is indicated in the tables. The sera obtained from these specimens were all titrated for their contents of diphtheria antitoxin in units per cubic centimeter according to a modification by Fraser[3] of the method described by Römer. This enabled us to ascertain more adequately the status of diphtheria immunity in these children and to make some observations on the amounts of antitoxin found as related to the Schick test readings.

From the Child Welfare Association of Montreal; the Departments of Pediatrics and of Public Health and Preventive Medicine, McGill University; and the Department of Epidemiology and Biometrics, School of Hygiene, University of Toronto.

SCHICK TEST AND SERUM ANTITOXIN

The Schick test has a limited application in the estimation of immunity to diphtheria. Its practical value in the determination of susceptibility to the development of clinical diphtheria is generally accepted. It is, however, quite inadequate quantitatively, as for example, in comparing the relative effectiveness of one diphtheria antigen as compared with another in the production of diphtheria antitoxin. When the test elicits a negative reaction in a person, it gives only some idea as to the lowest amount of antitoxin circulating in that person's blood stream; it is obviously unable to furnish any notion of the exact amount which is actually present; it may be just the lowest quantity necessary to produce a negative reaction or it may be any amount more than that.

In a number of investigations the workers have determined the amount of antitoxin present in specimens of blood obtained from persons upon whom Schick tests were performed and have attempted to correlate these with the results of the tests. There is no unanimity in the conclusions drawn from such investigations. Some have shown considerable variation in the antitoxin content of the blood in different persons who had negative tests, while others, although unable to draw a sharp line of demarcation, have nevertheless defined the limits of the range above which a negative reaction may be expected and below which a positive one usually occurs. Schick and Michiels[4] originally reported that $\frac{1}{30}$ (0.03) of a unit per cubic centimeter was the level above which a negative reaction and below which a positive reaction could be anticipated, and this figure has been quoted repeatedly.[5] Ramon and Debré[6] agreed that it was necessary to have at least this amount of antitoxin to give a negative reaction. Von Gröer and Kassowitz[7] obtained negative tests in two persons who had not more than $\frac{1}{250}$ (0.004) of a unit. Schick, von Gröer, and Kassowitz[8] stated that a Schick reaction became indefinite when the serum contained $\frac{1}{500}$ (0.002) of a unit and negative when $\frac{1}{200}$ (0.005) of a unit per cubic centimeter of serum was reached. Jensen[9] observed some children with less than $\frac{1}{2.000}$ (0.0005) of a unit per cubic centimeter of serum who gave negative Schick tests and concluded that the level at which a negative reaction is obtained represents considerable individual variation above and below $\frac{1}{30}$ (0.03) of a unit. Leach and Pöch[10] obtained negative reactions in a few children who had less than $\frac{1}{2.000}$ (0.0005) of a unit. Curth and Lorenz[11] concluded that a positive reaction was always associated with less than $\frac{1}{25}$ (0.04) of a unit, but a negative reaction gave no definite indication of the amount of circulating antitoxin. Glenny and Waddington,[12] working with guinea pigs, determined that a concentration of $\frac{1}{250}$ (0.004) of a unit per cubic centimeter of serum corresponds to the level at which a negative Schick reaction is elicited. Dudley, May, and O'Flynn[13] placed this level of immunity at $\frac{1}{100}$ (0.01)

of a unit. The results of Fraser and Halpern[14] and of Brandon and Fraser[15] indicate that a negative Schick reaction is obtained at about $\frac{1}{250}$ (0.004) of a unit. Parish and Wright[16] found that a person having as little as $\frac{1}{250}$ (0.004) to $\frac{1}{500}$ (0.002) of a unit per cubic centimeter of serum may have a negative reaction and in more recently made observations[17] they came to the conclusion that there is no definite level of antitoxin above which a negative reaction and below which a positive reaction to the Schick test may be invariably anticipated. They agree, however, that a negative reaction indicates a reasonably safe level of immunity, on the basis of the dramatic reduction of diphtheria in places where the susceptible children have been rendered actively immune to the extent that they showed negative Schick tests.

Okell[18] mentions the occurrence of negative reactions to Schick tests in thirty-five infants between the ages of 3 weeks and 6 months old, of whom twenty-nine had $<\frac{1}{500}$ (<0.002) of a unit and twenty-one had $\frac{1}{1.000}$ (0.001) of a unit or less per cubic centimeter of serum. It has been suggested that the skin of such infants may have greater tolerance for Schick toxin as a part of a general natural immunity.[13] Cooke[19] observed similar absence of cutaneous reactivity in infants to the Dick test.

Some reservations in comparing results are necessary on account of variable factors in the methods used by different observers, aside from the personal equation; for example, possible nonconformity of toxin used with standard requirements, the omission of the use of control injections or the use of toxin neutralized by antitoxin or heated toxin or diluted toxoid as control fluid in doing Schick tests, the time interval between the performance and the reading of the tests, and the time in relation to the tests when blood samples were obtained. Whether or not the variation of these factors entirely explains the discrepancy between the results, it would scarcely be justifiable to compare them unless it could be definitely ascertained that the conditions under which they were observed were uniformly identical, and this is by no means true of all the reports.

Table I shows the results of Schick tests according to the units of antitoxin per cubic centimeter of serum in blood samples obtained in the majority of the children on the fifth day (i.e., when the tests were read); in a few, nine days; and in another small group, seventeen days after the tests were done. Undoubtedly the levels of serum antitoxin at these times were higher in many instances than those which were present just before the tests were done. The relative number of reactions, indicated with a question mark, appears large. This is so because the vast majority of them which gave unquestionable results are not included in this paper, since, as was previously intimated, we were particularly interested in the children who manifested reactions which might be at all questionable. Of course, only the levels of antitoxin of the small number of children

TABLE I

SCHICK TEST REACTIONS AND ANTITOXIN TITRATIONS

TIME BLOOD DRAWN	RESULT OF SCHICK TEST	ANTITOXIN UNITS PER C.C. OF SERUM						TOTAL
		$<\frac{1}{500}$	$>\frac{1}{500}<\frac{1}{250}$	$>\frac{1}{250}<\frac{1}{100}$	$>\frac{1}{100}<\frac{1}{20}$	$>\frac{1}{100}<\frac{1}{5}$	$>\frac{1}{50}$	
Five days after Schick test	Negative			1	1		5	7
	? Negative	3		4	6	1	7	21
	? Positive	2	1		2		2	7
	Slightly positive	7	3	4	2		3	19
	Positive	14	6	4	2		1	27
	Total	26	10	13	13	1	18	81
Nine days after Schick test	Negative						2	2
	? Negative						3	3
	? Positive							-
	Slightly positive						3	3
	Positive						4	4
	Total						12	12
Seventeen days after Schick test	Negative						4	4
	? Negative							-
	? Positive							-
	Slightly positive						1	1
	Positive	1		1			1	3
	Total	1		1			6	8
Grand Total		27	10	14	13	1	36	101

All these children had injections of toxoid previously.

which were determined just before their tests were done could be correlated with the results of these tests. However, observations made at intervals after the tests were not without interest.

Titrations for antitoxin contents were carried out on sera from 101 children. The lowest titer for which they were tested was less than $\frac{1}{500}$ (0.002) of a unit per cubic centimeter of serum.

SERUM ANTITOXIN FIVE DAYS AFTER SCHICK TEST

None of twenty-six children with the lowest amount of antitoxin, $<\frac{1}{500}$ (<0.002) of a unit showed a definitely negative reaction. In twenty-one of them the reactions were positive, and in five they were listed as ?, three as ? negative, and two as ? positive.

Of ten who had $>\frac{1}{500}$ $<\frac{1}{250}$ (>0.002 <0.004) of a unit, nine had positive reactions, and in one it was ? positive. Of thirteen children who had $\frac{1}{250}$ $<\frac{1}{100}$ (0.004 <0.01) of a unit, the reaction was negative in one, ? negative in four, and positive in eight. Among forty-nine children whose sera contained $<\frac{1}{100}$ (<0.01) of a unit, one had a negative reaction; seven, ? negative; three, ? positive; and thirty-eight had positive reactions. Of thirty-two reactions in children whose titer of antitoxin was $\frac{1}{100}$ (0.01) of a unit or more, three with $\frac{1}{100}$ (0.01) of a unit were ? negative and one with this amount was slightly positive. Of the remainder, 6 were read as negative; eleven, ? negative; four, ? positive (one was a pseudoreaction); and seven, positive. The latter very probably had lower titers just prior to the test.

Some children who gave slightly positive reactions to Schick tests had lower titers of antitoxin than others whose reactions were more strongly positive, so that the intensity of the reaction to the Schick test was not necessarily proportional to the amount of circulating antitoxin.

SERUM ANTITOXIN NINE AND SEVENTEEN DAYS AFTER SCHICK TEST

Of twelve children whose Schick tests were read on the fifth day and from whom blood samples were drawn nine days after the tests were performed, four in whom the test was positive and one in whom the test was slightly positive had $>\frac{1}{50}$ (>0.02) of a unit, and two in whom the test was slightly positive had $>\frac{1}{20}$ (>0.05). It would seem reasonable to assume that the minute amounts of toxin and toxoid injected in performing the tests supplied the secondary stimulus to elevate the serum antitoxin to such high levels nine days later.[20] However, that the test itself may be inadequate as such a stimulus, even after a number of previous injections of toxoid, is demonstrated in a group of eight children whose tests were read on the fifth day and blood samples for antitoxin titration were obtained seventeen days after the tests. One child whose reaction was positive had $<\frac{1}{500}$ (<0.002) of a unit and another child whose reaction was positive had $\frac{1}{250}$ (0.004) of unit seventeen days after the tests. Apparently their antitoxin did not rise appreciably. In contrast with these, one child gave a positive reaction and yet had $>\frac{1}{50}$ (>0.02) of a unit and another whose reaction was slightly positive had $>\frac{1}{10}$ (>0.1) of a unit, seventeen days after the positive Schick tests.

Table II shows the results in fourteen children who were tested on two occasions at varying intervals from ten to twenty-three months. They had been given injections of toxoid more than a year prior to the first test. None of them received injections of toxoid or antitoxin or had had diphtheria in the interval. The tests were all read five days after they were done. Most of the first blood samples were drawn five days after the tests; in a few instances, nine and seventeen days, respectively, after the tests were done. The second samples were obtained just before the tests were performed. It is demonstrated that even the small stimulus provided in the Schick test and control is quite effective as a secondary stimulus. Antitoxic response to a relatively high level following the injection of a minute secondary stimulus has been well established.[21] It is also shown, as represented by the figures for the first three children in the table, that the previous injection of toxoid may act as an effective primary stimulus even though the level of antitoxin has been reduced to less than $\frac{1}{500}$ (0.002) of a unit. Five children who were previously positive became negative and showed high antitoxin titers. It is noteworthy that one child, who gave a negative reaction to the first test and had $>\frac{1}{50}$ $<\frac{1}{20}$ (>0.02 <0.05) of a unit seventeen days after the test, reverted to a positive reaction after nineteen months, and his second

TABLE II

TWO SCHICK TESTS AND TWO TITRATIONS (NO TOXOID IN THE INTERVAL)

FIRST TEST			SECOND TEST—BLOOD DRAWN BEFORE SCHICK TEST		
TIME BLOOD DRAWN	SCHICK TEST	ANTITOXIN TITER	INTERVAL AFTER FIRST TEST (MO.)	ANTITOXIN TITER	SCHICK TEST
Five days after Schick Test	Positive	<1/500	10	>1/50 <1/20	Negative
	Positive		11	>1/50 <1/20	Negative
	Positive		11	>1/50 <1/20	Negative
	Positive	>1/500 <1/250	10	>1/50 <1/20	Negative
	Slightly positive		20	<1/500	Positive
	? Negative	>1/250 <1/100	23	>1/10 <1/5	Negative
	Positive		23	>1/5 <1/2	Negative
	? Positive	>1/100 <1/50	19	>1/20 <1/10	Negative
	? Positive	>1/100 <1/20	11	>1/10 <1/5	Negative
	? Negative	>1/10 <1/5	10	>1/5 <1/2	? Negative
	Negative	>1 <2	10	>1 <2	Negative
Nine days after Schick Test	Slightly positive	>1/20	19	>1/250 <1/100	Negative
	Negative	>1/5 <1	19	>1/500 <1/250	Negative
Seventeen days after Schick Test	Negative	>1/50 <1/20	19	>1/500	Positive

titer or serum antitoxin was $<\frac{1}{500}$ (<0.002) unit per cubic centimeter. Two children (not included in Table II) who previously had positive reactions and had $>\frac{1}{50}$ (>0.02) of a unit nine days after this test gave positive reactions when retested nineteen months later and had $<\frac{1}{500}$ (<0.002) and $>\frac{1}{500}$ $<\frac{1}{250}$ (>0.002 <0.004) of a unit, respectively, in blood samples drawn five days after the second tests. One child who gave a negative response to a Schick test and had $>\frac{1}{5}$ <1 (>0.2 <1.0) of a unit nine days after the test was done gave a second negative reaction but had only $>\frac{1}{500}$ $<\frac{1}{250}$ (>0.002 <0.004) of a unit after nineteen months, while another whose test was slightly positive and had $>\frac{1}{20}$ (>0.05) of a unit nine days after the test was done became negative and had only $>\frac{1}{250}$ $<\frac{1}{100}$ (>0.004 <0.01) of a unit after nineteen months. Although the group is a small one, it demonstrates that some children whose circulating antitoxin has risen to a high titer following a minute stimulus may lose most of their antitoxic immunity in this interval.

An interesting experience was encountered in a 5-year-old boy. He received a first subcutaneous injection of 0.5 c.c. of diphtheria toxoid

at the age of 14 months, a second dose of 0.5 c.c. four weeks later, and a third dose of 1.0 c.c. five weeks later. When he was given a Schick test one year and four months following the third dose, the reaction was read as positive. A second Schick test after an interval of one year and ten months gave a similar reaction, and a sample of blood drawn on the fifth day after the test (when it was read) had $>\frac{1}{5}$ $<\frac{1}{2}$ (>0.2 <0.5) of a unit of antitoxin per cubic centimeter of serum. He was given 1 c.c. of toxoid. He was retested two months later, and a positive reaction was elicited at the site of the injected toxin, the control being negative. His titer of antitoxin was then 32 units. At the suggestion of Dr. D. T. Fraser, who very kindly had special solutions prepared, the boy was subjected to five intradermal injections of 0.1 c.c. each of (1) regular toxin, (2) regular control (1:100 toxoid), (3) special toxin which contained fresh toxin in such concentration that the toxicity was double that of regular toxin and with combining power slightly less than that of regular toxin, (4) special control which contained toxoid made from the same fresh toxin as that of special toxin and diluted to the same extent, and (5) special broth control. All, with the exception of the regular control, gave a marked reaction, the height of which was reached within twenty-four to forty-eight hours. After four days there were some slightly pinkish pigmented areas remaining about the four sites of reaction, and faint pigment was present a week after the injections were done. Sensitivity to some protein fraction, which was present in the toxin-containing solution and not in the regular control, was apparently responsible for a false reading of the Schick test.

Although such a discrepancy is undoubtedly very rare, it emphasizes the need for a uniform control solution which ideally should contain all the protein fractions present in the test solution, with the exception of the toxin.

SUMMARY

Reports concerning the level of antitoxin in persons below which a Schick test elicited a positive reaction and above which, a negative one, are discussed.

No child with $<\frac{1}{500}$ (<0.002) of a unit per cubic centimeter of serum up to five days after the test gave a definitely negative response to the Schick test. In three children with this low amount of antitoxin, Schick tests were read as ? negative and in two, as ? positive. The lowest titer of antitoxin five days after the test, which was associated with an unquestionably negative reaction, was $>\frac{1}{250}$ $<\frac{1}{100}$ (>0.004 <0.01).

Some children who showed faintly positive reactions to the test had lower titers of antitoxin five days after the test than others in whom more strongly positive reactions were observed.

The Schick test and control injections did not act as a satisfactory antigenic stimulus in two children who had positive reactions after

previous subcutaneous injections of diphtheria toxoid, their titers of antitoxin being low seventeen days after the positive tests.

Two children who had positive reactions in spite of previous subcutaneous injections of diphtheria toxoid but who responded rapidly and to a high level of antitoxin following the Schick test and control injections returned to a low level within a period of nineteen months.

A falsely positive reaction was encountered in a child who had 32 units per cubic centimeter of serum; this was apparently due to skin sensitivity to a protein fraction which was present in the test solution and not in the control.

We wish to express our appreciation and thanks to Dr. D. T. Fraser, Associate Director of Connaught Laboratories, University of Toronto, for valuable comments, and for the titrations of antitoxin which were carried out at Connaught Laboratories under his supervision.

The dilutions of toxin and toxoid which were employed were prepared and tested by the Connaught Laboratories, University of Toronto.

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FETAL TOXOPLASMIC ENCEPHALITIS—A TYPE OF CONGENITAL CEREBRAL DISEASE

PAUL M. LEVIN, M.D., AND HALCUIT MOORE, M.D.
DALLAS, TEXAS

WITHIN the past few years, due chiefly to the clinicopathologic studies of Wolf and his associates,[1] a new clinical entity has been described. It is an inflammatory disease of the central nervous system caused by a protozoon, *Toxoplasma hominis*. Although human infection with this organism occurs at all ages of life, its most serious consequences result from infection of the young infant or fetus. At this age it is often fatal, the most prominent pathologic findings being disseminated necrotizing lesions of the brain and choroid layer of the eyes. The cerebral lesions usually become calcified, and the eye grounds show massive areas of chorioretinitis. In surviving patients the clinical manifestations consist of retardation of mental and neural development and the convulsive state.

The following is a description of a case we have observed, presenting the characteristic clinical picture of fetal toxoplasmosis: intracranial calcification, mental retardation, convulsions, and chorioretinitis.

G. F. H. was born on Aug. 11, 1940, after an easy spontaneous delivery. There was no asphyxia or jaundice. The mother had previously had *Trichomonas vaginalis* vaginitis, but this had subsided before this, her first pregnancy. The prenatal care had been thorough, the only maternal illness being a mild attack of coryza in the eighth month of pregnancy. Fetal activity began at four and one-half months and was vigorous throughout the remainder of the pregnancy. The circumference of the head at birth was twelve and three-fourths inches. At the age of 1 month the infant developed a skin lesion which was considered to be atopic dermatitis of mild degree and which promptly improved under ointments and ultraviolet irradiation. At 2 months of age his gums became swollen but the teeth did not erupt until the age of 9 months. Otherwise he seemed to be normal and grew rapidly until he had his first convulsion at the age of 3½ months.

At this time, on Nov. 24, 1940, he had a sudden attack of retraction of the head and cyanosis for a few seconds. This was followed several hours later by a series of four generalized convulsions, with extensor rigidity of all extremities, opisthotonus, staring of the eyes, and apnea with cyanosis. Each lasted about one minute and was followed by stupor and crying for an hour. He became irritable; jarring of the bed seemed to make him jump, stiffen his extremities, and clench his fists.

The general physical examination yielded normal findings. Roentgenograms of the skull showed several areas of increased density within the cranial shadow. Other laboratory tests, including urinalysis, determination of the calcium and protein content of the blood, and intracutaneous tuberculin tests, gave negative results. The Wassermann reactions of the blood of both the patient and his mother were likewise negative.

From the Departments of Neuropsychiatry and Pediatrics, Baylor University College of Medicine.

The attacks were somewhat irregular. There were frequent minor seizures, resembling a startle pattern with momentary elevation of the arms. In the severe attacks, which began with a cry and loss of consciousness, he showed apnea, cyanosis, twitching of the face, and either flaccidity or rigidity of the extremities lasting one minute. These seizures usually occurred shortly after awakening, at intervals of three or four days. Minor spells were more frequent for a day or so before each convulsion.

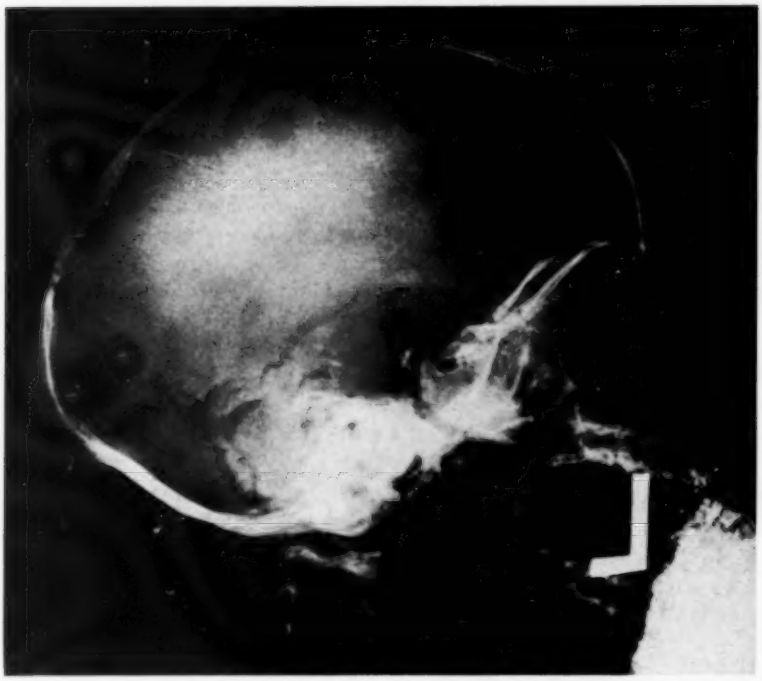

Fig. 1.—Roentgenogram of the skull, right lateral projection, showing the multiple areas of intracranial calcification.

On Dec. 25, 1940, he was anesthetized for more adequate examination. The ocular fundi were examined but were thought to be normal except for an elliptical shape of the discs. Spinal puncture yielded fluid under a normal pressure and containing a slight excess of protein but a normal amount of cells. Additional stereoscopic roentgenograms of the skull were made (Fig. 1). These clearly showed the intracranial positions of the calcified areas. There were three clusters of opaque particles in the left precentral region, one cluster in the right anterior temporal region, a horizontal linear shadow at the base of the left temporal lobe, and a vertical linear shadow in the midline, fanning out above as if it represented part of the falx cerebri.

Three days later he had another convulsion and was placed on phenobarbital, ¼ gr. (0.015 Gm.) five times daily. The spells became milder but no less frequent. Doubling the dosage of the phenobarbital only made him more drowsy. As the results of this treatment were scarcely satisfactory, he was placed on dilantin (given in daily doses as high as 0.16 Gm.). He then became more alert, but the

spells were more severe. A combination of both drugs seemed to give a little better result than either given separately.

The family history yielded no cases of convulsive disorder or mental disease in three generations. The paternal grandmother had had migraine. Roentgenographic studies of the skulls of the mother and father gave normal findings.

Neurologic examination on Jan. 24, 1941, showed a fairly alert infant, aged 5½ months. He held his head up at times but could not sit alone. The head was slightly small in relation to the body size, as it had been all his life. A generalized spasticity of moderate degree was present, predominantly of the flexors of the arms, and adductors of the thighs. The tendon reflexes were lively, and there was fairly well sustained ankle clonus. The plantar responses were extensor. The pupils were equal and reacted well to light. The fundi showed pallor of the nasal portions of both optic discs and several large areas of old chorioretinitis (Fig. 2). These were located in the lower temporal portion of the right fundus and in the upper temporal and lower nasal portions of the left. They were all sharply outlined and showed yellowish white patches with accumulations of pigment, chiefly at their margins, but also within the atrophic areas. The vitreous was clear, and there were no hemorrhages or areas of edema in the retina.

Fig. 2.—Photograph of the left fundus. Scattered areas of choroidal atrophy and pigmentary accumulations.

An electroencephalogram was made at this time, with leads placed over the central region of both sides. The dominant rhythm consisted of waves occurring at a rate of 3.5 cycles per second, usually synchronous on the two sides. Two clinical minor attacks took place during the recording, each lasting about one second. During the attacks there was a synchronous onset of irregular waves of high voltage, some of which were sharp; the fully developed wave-and-spike complex characteristic of petit mal in older patients was not seen (Fig. 3). Random waves, singly or in pairs, of high voltage also occurred at periods when there was no clinical indication of a seizure.

In April, 1941, the convulsions became more frequent, occurring daily. He was placed upon sodium bromide, 15 gr. (1 Gm.) daily in divided doses, and the phenobarbital and dilantin were discontinued. After two days the attacks decreased greatly in frequency. During the following twelve months he had only three major attacks, the first after an interval of six months. Minor seizures have also been less frequent. His neuromotor development has, however, been seriously retarded. At 20 months of age he was unable to hold his head erect for more than 15 seconds without support, nor was he able to express himself by words, although his mother described expressive responses by gesture. Some visual perception seemed to be present. Microcephaly was now a definite finding (Fig. 4).

Fig. 3.—Electroencephalogram. High-voltage waves in both central regions occurring during a minor convulsive attack.

Fig. 4.—Photograph of the patient at the age of 16 months. Microcephaly.

The diagnosis of this case offered considerable difficulty. Tetany was first suspected but was promptly excluded on the basis of normal chemical findings. The intracranial calcified lesions raised the possibility of multiple vascular anomalies of the brain, such as those found in some cases of convulsive disorder.[2] When the areas of chorioretinitis were discovered, it was felt that both the brain and choroidal lesions were a part of a disseminated focal disease, presumably infectious. We

were at a loss as to the etiology of this condition until we came across the report of the identical syndrome in infantile (fetal) toxoplasmosis.[3] Laboratory tests for this disease were performed by Dr. Albert B. Sabin at the Children's Hospital, Cincinnati, to which city the patient and his family moved in August, 1941. Dr. Sabin has summarized the results of these tests in Table I.

TABLE I

TOXOPLASMA COMPLEMENT FIXATION WITH H. SERA

NAME	SPECIMEN	TOXOPLASMA ANTIGEN +					CONTROL ANTIGEN +				
		UNDIL.	1:2	1:4	1:8	1:16	UNDIL.	1:2	1:4	1:8	1:16
G. H. (Patient)	Oct. 21, first test	++++	++++	++++	++++	±	0	0	0	0	0
	Oct. 21, second test	++++	++++	0	0	0	0	0	0	0	0
	Dec. 5	++++	++++	++++	++++	±	0	0	0	0	0
Mrs. H. (Mother)	Oct. 21, first test	++++	++++	+	0	0	0	0	0	0	0
	Oct. 21, second test	++++	0	0	0	0	0	0	0	0	0
	Dec. 5	++++	++	0	0	0	0	0	0	0	0
Mr. H. (Father)	Dec. 5	0	0	0	0	0	0	0	0	0	0

Toxoplasma antigen: Saline extract of frozen and thawed infected rabbit brain.
Control antigen: Saline extract of frozen and thawed normal rabbit brain.

Additional information was sought concerning the possible acquisition of a toxoplasmic infection. It was learned that the family cat (Persian variety) had been sick several weeks before the patient was born. The symptoms of this illness were weakness, vomiting, loss of appetite, and a temperature of 108° F. A relapse occurred shortly after this illness. Finally the cat appeared to have recovered and was given away. Investigation revealed that the cat was found dead in August, 1941, and was cremated. Many wild rabbits lived in the neighborhood of the patient's home, and several young ones had been killed by this cat.

COMMENT

An early onset, probably intrauterine, of the disease in this patient is suggested by the following factors: The cerebral lesions were calcified at the age of 3½ months and, judging by their appearance in later roentgenograms, they were already completely healed. The areas of chorioretinitis, when discovered, also gave the appearance of a quiescent stage. A mild microcephaly was present since birth, and the degree of this condition did not change as the patient grew older. Finally, serologic evidence of infection in the mother but not in the father is consistent with the possibility of prenatal infection.

Before the discussion of toxoplasmosis, comment upon and qualification of the serologic tests should be made. Both complement fixation and rabbit protection tests were carried out by Dr. Sabin. Specific complement fixation antibodies were consistently demonstrated in several specimens of blood from the patient and mother. However, no neutralizing antibodies were detected by rabbit tests made with the same blood samples. This discrepancy is unusual. As Dr. Sabin wrote us (Jan. 15, 1942):

"Such a situation has not been encountered before in our work with toxoplasma. Our experience has rather been the reverse; namely, that

the complement fixation tests appeared to be either less sensitive or could be obtained less frequently than the neutralization test. Thus we have a considerable number of sera which have neutralizing antibodies for toxoplasma but no complement fixing antibodies. Thus far, the H. sera are the only ones in which the reverse obtains. Because of this peculiar behavior of these sera, I am not prepared to say, although the complement fixation test appears to be specific to the best of our knowledge, that the results obtained with the serum of the child and the mother represent unequivocal evidence of toxoplasmic infection some time in the past."

From a clinical standpoint the findings in this case are entirely typical of toxoplasmosis of prenatal inception. The effects of this infectious process seem to differ according to the age at which infection occurs. Of 17 cases of this disease that have been reported prior to this case, eleven had an onset of clinical manifestations either at birth or shortly thereafter[4]; in nine of these, death had occurred, and the diagnosis was established at autopsy, while in the remaining two the patients were still living at the time of the report. These eleven infantile cases presented a symptomatology that was strikingly uniform and, to our knowledge, specific for toxoplasmosis. Focal areas of necrosis of the brain which usually became calcified were present in all cases. These resulted in microcephaly unless, as happened in several instances, there was an associated stenosis of the aqueduct of Sylvius with obstructive hydrocephalus. Convulsions were almost uniformly present, as was mental deficiency. In one instance there was a necrotic lesion of the spinal cord, with microscopic foci in other cases. In addition to the encephalitis or encephalomyelitis, there is usually also a focal necrotizing chorioretinitis. These lesions are massive, larger than those seen in cases of disseminated chorioretinitis of congenital syphilis. In one instance there was an unilateral microphthalmia. General pathologic observations in the few cases with complete autopsy included widespread dissemination of the toxoplasma in one case and scattered areas of inflammation of striated muscle, including the myocardium, in two others.

Onset in childhood was seen in two cases of this disease.[5] In both there was a brief illness with convulsions, mental confusion, and a mononuclear pleocytosis of the cerebrospinal fluid. Recovery without evident residual defect (at least not for a period of several months), took place in one case, and in the other the child died and showed at autopsy (which was limited to the brain and spinal cord) microscopic foci of necrosis and irregular cellular infiltrations. Three instances of the disease have been described in adult life,[6] with clinical features simulating the typhus-spotted fever group. A maculopapular eruption of the skin, weakness, and fever were present in all three. In one case the patient became markedly cyanotic and irrational and died in coma two days later. A second patient became irrational and deaf.

Autopsies of these cases showed minute areas of necrosis in various organs, with rare microscopic inflammatory lesions in the brain. Parasites were found throughout the body, notably in aggregates within myocardial fibers.

Toxoplasmic infestation is more common in man than would be judged from the paucity of the reported cases of the clinical disease, since the mothers of children with infantile toxoplasmosis may show immune bodies in their blood.[3] How widespread the toxoplasma parasite occurs in man remains to be studied.

SUMMARY

Fetal toxoplasmosis is a cause of focal encephalitis, with intracerebral calcification and chorioretinitis. The residual symptoms are convulsions and retardation of mental and neuromotor development. A case is presented with this characteristic clinical picture. Specific complement fixing antibodies were demonstrated in the blood of the patient and mother.

We wish to thank the following physicians for observations which they kindly made after the patient's removal to Cincinnati, Ohio: Dr. Albert B. Sabin, immunologic tests; Dr. D. J. Lyle, photograph of retina; Dr. C. R. Ritershofer, clinical observations.

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1711 Pacific Avenue
4105 Live Oak Street

IMMEDIATE FATALITY FOLLOWING THE USE OF MERCUPURIN

JOHN VAUGHN, M.D.
SANTA MONICA, CALIF.

SINCE the introduction in 1920[1] of mercurial diuretic compounds for intravenous injection, a voluminous literature testifies to the safety of these drugs even over extended periods of time.[2] However, occasional reports of immediate alarming and sometimes fatal reactions are noted. Wolf[3] reported one instance of sudden death, anaphylactic in nature, immediately following the intravenous injection of salyrgan in a child 4 years of age. Sundaram[4] reported an alarming immediate reaction in a patient 10 years old following the intravenous administration of 0.5 c.c. of salyrgan diluted in 10 c.c. of distilled water. His report is not clear as to whether the reaction was fatal. Hug[5] described a rapidly fatal reaction following the use of salyrgan in a case of severe cardiac myodegeneration with hepatic cirrhosis. Parade[6] cited his case of threatening disturbance following the injection of salyrgan and recommended caution in the use of the drug in cases of coronary disease in which myodegenerative processes exist. He advised a small initial trial dose of 0.5 c.c. intramuscularly. Cadbury[7] quoted several of the earlier reports cited above, and added four cases of serious reactions, two of which were fatal, following the intravenous injection of salyrgan. Derow[8] and Rosenthal[9] each reported an instance of acute mercurial intoxication following the use of salyrgan. Their patients did not succumb in immediate and dramatic fashion, and at autopsy the lesions typical of mercurialism were found. Apparently the mode of death in these instances differs from that in other reported cases and probably represents a separate variety of fatal reaction.

The majority of earlier reports were concerned with the use of salyrgan, perhaps because of more frequent use of this agent in former years. Later reports have implicated other mercurial diuretics. Greenwald and Jacobson[10] reported two instances of sudden death in small children suffering from nephrosis who had received neptal* by intravenous injection. More recently, fatality has been recorded from the use of mercupurin[11, 12] and esidrone.† Tyson[11] stated that the only fatalities recorded to the date of her case reports were concerned with the nephrotic syndrome. Others[12] subsequently encountered sudden fatality from the intravenous use of mercupurin in three cases of congestive heart failure.

*Hydroxy mercury propanol amido carboxy phenoxy acetic acid (Wallan).
†Pyridine dicarboxy β mercuri hydroxypropylamide-theophylline (Ciba).

Several authors have suggested caution in administering the first dose of a mercurial diuretic, and some have recommended that the drug be given well diluted in distilled water to lessen the likelihood of reaction. However, the majority of fatalities have been recorded in patients who had received one or more previous injections without apparent reaction. The following report adds another case in which an immediate fatality occurred.

R. L., a boy 16 years of age, had been cyanotic since birth. His progress and general health during childhood were uneventful except for extreme cyanosis, dyspnea on moderate exertion, and pronounced clubbing of the digits. He remained ambulatory and fairly active until July, 1939, when edema and progressive congestive myocardial failure developed.

Physical Examination.—The patient was a poorly nourished lad, 16 years of age, suffering from dyspnea and orthopnea. The mucous membranes, ear lobes, and extremities were deeply cyanotic. Peripheral edema without an ascites or hydrothorax was present. There was marked pulmonary hypertrophic osteoarthropathy. The heart was considerably enlarged. A systolic murmur was heard over the entire precordium. In the third and fourth left intercostal space near the sternum, a diastolic murmur was noted. Blood pressure was 110/65.

Laboratory.—Repeated urine specimens were normal except for slight albuminuria. The electrocardiogram revealed extreme right-axis deviation with total inversion of the QRS complex in Lead I. The P deflections were large and pointed, measuring 5 mm. in amplitude in Lead II. Normal sinus rhythm was present, and the conduction was normal. The record was considered typical of congenital heart disease.

The patient was treated by thorough digitalization, and at various times several diuretics of the xanthine group were given orally. Fluids were restricted, continuous bed rest was instituted, and mild sedatives were prescribed as necessary.

On several occasions during the last few weeks of the illness the patient complained of fairly severe epigastric pain of one to several hours' duration which subsided spontaneously. The pain was unattended by any other symptoms. Blood pressure determinations remained unaffected.

Diuresis was unsatisfactory, and evidence of digitalis intoxication developed in the form of nausea and pulsus bigeminus. This was confirmed by electrocardiogram on Sept. 9, 1939. After consultation,* it was agreed to stop the use of digitalis temporarily, and the patient was given ammonium nitrate tablets in the amount of 90 gr. daily for two days in preparation for the use of mercupurin.

When seen at his home on the morning of Sept. 12, 1939, the patient was comfortable and in good spirits and somewhat improved in general condition. Two cubic centimeters of undiluted mercupurin were very slowly administered by vein. Within one minute after completion of the injection, the boy seemed in distress, sat upright, and complained of severe lumbar pain. While an injection of epinephrine was being prepared, severe expiratory dyspnea appeared, the external jugular veins became distended, and within three minutes from the onset of the disturbance, respirations and cardiac activity had ceased in spite of the intracardiac injection of epinephrine solution, and artificial respiration was given.

Necropsy Report.—Because of time limitation, organs other than the heart and great vessels were not examined in detail, but gross inspection showed no abnormality except chronic passive congestion.

The heart weighed 500 Gm. Both ventricles were greatly hypertrophied. Section revealed two areas of myocardial infarction in an advanced stage of healing,

*Consultation was with Dr. Lewis T. Bullock, to whom the author is indebted for advice in the preparation of this report.

one in the left ventricle near the apex, involving the septum and measuring 3.5 cm. in diameter, and a smaller area in the right ventricle near the base measuring 0.5 cm. in diameter. The coronary vessels were patent. The endocardium of the left ventricle near the apex was covered with a shaggy, firm ante-mortem thrombus, the central portion of which was brown and somewhat degenerated in appearance.

The anomaly present was pulmonary atresia with patent interventricular septum and patent ductus arteriosus. The aorta communicated with both ventricles, and three aortic cusps were present. From the aortic arch, 4.5 cm. from the aortic ring, a funnel-shaped ductus arteriosus opened through an orifice 3 mm. in diameter into a communication with the right and left pulmonary arteries. The left pulmonary artery attained circumference of 4 cm.; the right pulmonary artery was dilated to 6.5 cm. in maximum circumference.

The anomaly probably is explainable on an embryologic basis* by complete absence of the pulmonary component after division of the truncus.

COMMENT

It is remarkable that the patient survived for sixteen years handicapped by such extreme defects in the pulmonary circulation. The occurrence of myocardial infarction without coronary artery occlusion has been noted.[13] As previously observed, for several weeks prior to death the patient had complained of epigastric pain. The occurrence of infarction was not revealed by a three-lead electrocardiogram, recorded a few days before death, and was an unsuspected finding at necropsy.

In view of the relative paucity of reports of fatal reactions in comparison with the wide use of mercurial diuretics, it seems that immediate fatality is fortunately rare. The majority of reports attribute death to immediate collapse, anaphylactic in type. Salyrgan has been implicated in most cases, but recently mercupurin has been apparently responsible in the few cases reported above.[11, 12] Other unreported fatalities may have occurred.[14]

In the case herewith reported, the heart was the seat of extensive damage. The possibility of embolism or other causes of death unrelated to the use of mercupurin might be considered, but the sequence of events at the time of death leads to the conviction that idiosyncrasy to mercupurin was responsible. It is to be emphasized that on the day of injection, the patient was generally improved in comparison with his previous condition.

SUMMARY

1. Immediate fatality of an anaphylactic nature following the injection of mercupurin is reported in a case of congenital heart disease with congestive failure.

2. In view of other reported fatalities, caution should be exercised in the use of mercurial diuretics in seriously ill patients.

*The pathologic study was performed by Dr. H. A. Edmondson of the Department of Pathology, University of Southern California School of Medicine, Los Angeles.

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American Academy of Pediatrics

Proceedings

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS., OCT., 9-11, 1941

Round Table Discussion on Behavior Problems

Chairmen: Horton Casparis, M.D., Nashville, Tenn.
Douglas A. Thom, M.D., M.S., Director, Habit Clinic for Child Guidance; Professor of Psychiatry, Tufts Medical School, Boston, Mass.
James S. Plant, M.D., Director, Essex County Juvenile Clinic, Newark, N. J.

Associates: C. Anderson Aldrich, M.D., Chicago, Ill.
George E. Gardner, Ph.D., M.D., Co-Director, Judge Baker Child Guidance Clinic; Assistant in Pediatrics, Harvard Medical School, Boston, Mass.
Harold H. Mitchell, M.D., Astoria, N. Y.
Samuel W. Hartwell, M.D., Professor of Psychiatry and Mental Hygiene, University of Buffalo Medical School; Director, Child Guidance Clinic, Children's Hospital, Buffalo; Snyder, N. Y.

Secretaries: John C. Montgomery, M.D., Detroit, Mich.
Norman T. Welford, M.D., La Grange, Ill.
George F. Patterson, M.D., Cincinnati, Ohio.

CHAIRMAN CASPARIS.—Round table discussions on behavior problems such as this, which were conducted a few years ago, were led by psychiatric discussants, whom we felt it necessary to call in. As an indication of our own education and development, you will note that we are now trying to take over and discuss these problems ourselves. There is a tremendous interest in the subject of behavior problems, and we must learn to assume the responsibility.

I believe it would be best to speak of mental health rather than mental hygiene. By behavior we mean what an individual does and does not do, what he says and does not say. The *end* results of abnormal behavior are always seen by physicians, but there is a long prodromal stage. We must get as far back as we can. The structure of healthy behavior is known and can be compared to building a house. We have, *A*, the material which goes into building it, and, *B*, the way it is built.

A varies—it is what we think of as inheritance. *B* is the foundation; that is, the uprights and so forth, and the principles of construction can be compared to the environment.

I would like to advance a crude definition of life. Life is trying to get what we want and avoid what we do not want. But wants vary.

Let us list some universal wants or basic needs.

1. Courage: every child starts with a bank account of courage which can be increased by facing the problems as they arise and can be depleted by overprotection.
2. Relaxation; that is, play.
3. Reproduction.
4. The need to obey simple laws, which are primarily a development of the Golden Rule.
5. Security, which can be subdivided into (1) physical and (2) social security.
6. There must be a goal; that is, a feeling things are getting better.
7. Recognition.

DR. ALDRICH.—In considering the subject of infant behavior, it is most important to realize that its significance changes with the growth of a baby's abilities in the motor, mental, and emotional fields.

During the *neonatal period,* up to three months, we find him reacting for the most part in a reflex, subcortical manner. Cortical function begins at 4 to 8 weeks, but is adequate in a very limited field only, for many months after this. This reflex behavior is designed for protection and survival and governs such activities as feeding, sleeping, and eliminating. He protests with his cry any threat to physical comfort or well-being. This is a logical reason for adult respect for infant rhythms such as schedule for feeding, sleeping, and eliminating. No baby acting on a subcortical level is ready for bowel training. It also is a reason for investigating the cause of crying, such as heat, cold, wet, pain, fear, hunger, or need for fondling.

It should be axiomatic that spoiling is impossible before the development of the cortical functions. The mechanism of early spoiling is neglect of needs rather than overindulgence. Looked at from this angle, adults often present the behavior problem instead of babies. It is negativism to fail to respond to a child's basic needs. Twenty-five years' experience has taught me that responsive adults breed responsive babies, and that rigid disciplinarians of babies at this age breed spoiled, unhappy children with no confidence in themselves or their parents.

In the *three to six months' period,* behavior begins to be conditioned by (a) experience with the world, satisfying or frustrating; (b) development of adequate vision with its associated brain tracts; (c) development of motor control, head, neck, and arms; and (d) socialization through the smile and laugh. As a result of these growth changes, several definite advances take place. First, his compulsive behavior of protection is markedly modified, leading to his greatest change in personality. The direction varies according to his individual experience. Second, he begins to show curiosity in the surrounding visual objects. Third, he capitalizes on his ability to help himself by holding his bottle and by accepting semisolid food in a spoon. Fourth, he is introduced to play, his greatest educational facility. Fifth, these activities result in his leaving behind such infantile activities as the reflex grasp, thumb sucking, Moro and tonic neck reflexes, etc. It is obvious that the adult response to this developmental period can push ahead or delay all these desirable ends. Attention here aids growth, does not spoil children.

During the *last eight months of the first year* his behavior is changed by tremendous motor progress in hand control and posture so that he gains voluntary control of all extremities and the ability to roll over, sit, crawl, stand, and sometimes walk. In addition, his mental development makes possible the use of words, imitation,

conditioned behavior, coordination of ideas and activity. Another interesting development is a fear of strange sights. Everything new, particularly if it takes him away from his mother, is a threat. This attitude continues up to the end of the second year and is normal behavior. During this time, also, most children gain voluntary control over their bowel movement. Here again our adult function is to synchronize our efforts with a baby's difficulties; to support the baby's development and give him a feeling of security.

DR. MITCHELL.—You appreciate that when your patients start in school they are exposed to an entirely new set of influences. The reactions of children to their school world may be very different from their reactions in the home. In some cases the pediatrician finds it necessary to interview the teacher in order to get a complete picture of the behavior of the child, but such thoroughness in history taking is not always practical. It may be very difficult to interview the teacher and so only part of the child's behavior pattern is understood. I should like to emphasize that the doctor and nurse in school can usually be of great help to you in obtaining information about what your patient is like while he is in school. They can interview the teacher easily, and in many cases the teacher is more objective and more likely to evaluate behavior symptoms accurately than the average parent.

If a mother is not aware of the school behavior of her child, the doctor may miss the most important part of the history. School behavior may be the key to the diagnosis. I remember a little girl of eight years who had been carefully studied by her pediatrician to get at the cause of enuresis. He had tried about everything with no results until it was discovered that her school behavior was distinctly different from her home behavior. At home she cried more easily. She was likely to be anxious or peevish and babyish. She was easily upset when her older sister got the best of her. This difference in behavior gave the clue that was needed to recognize that the maid, who had cared for the child since infancy, was overprotecting and interfering with the child learning courage and self-reliance. The doctor had not obtained a clear picture of the most significant behavior of the child because the mother had not appreciated how much the maid was babying and protecting the child. The infantile patterns and the retreat from competition with the older sister in the home became apparent only when the home behavior was distinguished from the school behavior. This difference between school and home behavior indicated the treatment that was needed. The maid got another job. The child was given some responsibility for care of pets; she went to camp, and she made a very satisfactory adjustment.

The child who does not like school, the child with a reading disability, or the child with anxieties may present a problem that is distinctly a school problem and yet it often occurs that there is no exchange of information between the school and the practicing physician. When the members of the Academy were asked in 1937 about their relations to the school health service, 96 per cent expressed some dissatisfaction with the service and 75 per cent of the replies indicated that the pediatricians had not had any requests for recommendations concerning their patients in the school. Probably many physicians have not thought about getting information from the school, and the school people have made little effort to let the practicing physician know that they would be glad to cooperate. I am sure from my knowledge of school health workers that almost always the nurse or doctor in the school would appreciate being asked to find out about a child from the teacher and to report information to the private physician. This should make it easy for the practitioner to get the information he needs to understand the school behavior of his patients.

The cardiac child is particularly likely to get into difficulty if there is no exchange of information between the doctor and the school. Usually when the practitioner allows a child to return to school after an attack of rheumatic fever,

there is danger of either overprotection and excessive restrictions or there is neglect of the extra rest and medical supervision that is recommended. Usually if the teacher knows only that the child has "some heart trouble," she fears that he may drop dead from overexertion. When the doctor advises "limited activity," she is likely to limit the child so much that he becomes excessively timid or else resentful. A diagnosis of heart disease from a private physician is often used by children to avoid "gym work" when the physical education program might contribute much to the child's mental health. If there is not a clear understanding by the school people as to the meaning of the diagnosis, and what the child should and should not do, then the cardiac label is likely to contribute to emotional instability or else a resistance to all health protection. If resistance develops, both the parents and child get the notion that the advice of the physician is not very important. This attitude of resistance to medical advice is almost invariably due to some confusion in the approach to the parent. The school contributes to the parent's confusion when the school physician does not know the diagnosis of the practitioner and does not interpret the case to all the school people who must deal with the child and his parents.

The warning against the danger of upper respiratory infections is often interpreted as a need for a kind of coddling rather than that the child should stay home and in bed when he gets such an infection. Of course the nurse can see that such a child gets sent home promptly if the parent should allow the child to come to school with a cold. Whenever a doctor makes a recommendation to the school concerning restrictions or individual consideration to be given to a child, he should know whether the school will or can carry out his advice. Large school systems are likely to labor under administrative limitations. The practitioner is not always aware of the stair climbing, recess activities, pressure and competition that his patient may be exposed to by the exigencies of school administrations. If the practitioner reports the diagnosis and classification according to that of the American Heart Association, then the physician in the school can interpret the child's condition to the school authorities and advise the practitioner as to the best adjustment that can be offered to the patient. If the school physician knows the approximate date of the next appointment, he can direct the nurse to give such a follow-up as is necessary to see that the child continues under medical supervision.

When a child has a hearing handicap, there is a similar need for exchange of information between the practitioner and the school. The parent may accept the physician's advice in his office, and then later reject the whole idea that the child is hard-of-hearing, needs lip reading, a special seat in school, and extra protection when he has a cold. Neighbors and friends often maintain a continual barrage of well-meant but misleading advice, and a mother may be quite unwilling to accept her child as he is. She may not understand that she should find out what he can do, and help him to succeed. Here again a report to the physician in the school concerning the diagnosis and the needs of the child is necessary in order that the school people may support the practitioner in what he is trying to do for the mental health of his patient. Not only does the teacher and principal influence the mental health of the child in school but they often advise parents. If members of the school staff have had a clear interpretation of the case, they may guide the parents wisely. In the case of a handicapped child, members of the school staff are particularly likely to influence decisions of parents when parents get discouraged, or depend on false hopes, or consider quack treatment. The members of the school staff can certainly contribute to an adjustment which helps the child to develop his abilities so as to overcome as far as possible the effect of his handicap.

Certainly the management of any handicapped child should help him learn to live with his handicap, to compete with his peers, and to know what he can do well and develop self-reliance. No matter how well the physician may prepare the

mother and the whole family to understand the child's condition and his needs, the school environment can upset the best-laid plans. Teachers, principal, and school companions can seriously interfere with the child's adjustment unless some one can interpret the case to members of the school staff and advise them of the child's needs. This function of interpreting the *whole* child to the teachers and to all who influence the mental health of the child in school is probably the most important job of the physician in the school. He should make it easy for the practitioner to have support in carrying out his advice for the improvement of the mental health of his patients.

CHAIRMAN THOM.—On many occasions I have emphasized the fact that the pediatrician is in a strategic position to guide and direct the personality development of the child. Of all varied specialists, his position is unique because of his continuity of service and the influence which he may exert, not only upon the child, but also on the child's environment. Pediatrics has already demonstrated in a manner most convincing the importance of the early years in laying the foundation for physical health and thereby not only reducing infant mortality, but also increasing physical fitness during adolescence and adult life. The pediatrician's contribution has been well stated by Stieglitz* in the following paragraph:

> Prophylactic pediatrics has contributed greatly to increasing life expectancy. Not only has there been a vast improvement in the curative therapy of pediatric disease, but the pediatricians have done more than any other group of physicians to advocate and apply individual preventive medicine. By better feeding of presumably healthy babies and by prophylactic immunization, they have made healthy children healthier. The pediatrician has recognized that health is more than the mere absence of disease, that there are degrees of health. Such prophylactic practices have not only reduced infant and juvenile mortality, but have also unquestionably prevented many chronic sequelae from childhood ills. It is worthy of emphasis to note that marked advances in pediatric knowledge followed recognition of the fundamental concept that the child is not merely "*the little man,*" but presents nutritional, immunologic, functional, and structural problems and characteristics peculiar to infancy or childhood or both.

If it were possible for pediatricians to incorporate into their teaching and practice such mental hygiene disciplines as are available and of proved worth, another epoch-making contribution would be made to the field of preventive medicine.

Notwithstanding the fact that the pediatrician tends to be organically minded in his outlook on medicine, seeking the solution of his problems in changes in structure, physiologic imbalances, and tangible evidence of the physical signs, laboratory tests, and the x-ray, he has evidenced an interest in the psychologic and psychiatric concepts and has been receptive to this approach in the interpretation of disturbed function and behavior during the preadolescent years. During these early years, we frequently find that conflict in the emotional field expresses itself in a more direct and less well-disguised manner than it does during the adolescent period. The behavior of a young child is less likely to be influenced by education, training, and experience. The child's responses are more primitive, instinctive, and socially crude. The emotional reaction to conflict has not the same need of being converted into behavior patterns as would be acceptable to one who is more mature, more highly socialized, and who is concerned with the idea of conformity and the approbation which it brings.

*Stieglitz, Edward J.: The Potentialities of Preventive Geriatrics, New England J. Med. 225: 247, 1941.

The child at 5 years of age who is frustrated because of jealousy may sulk or make an attack on the object of his jealousy or utilize obvious ways of getting attention, while the 16-year-old girl, who is suffering from the same frustration and emotional disturbance, may develop what appears to be obscure physical symptoms—neurosis, vomiting, headaches, insomnia, gastrointestinal disorders, or perhaps some unexplainable phobias. Psychologic causes and effects become less obvious as the mental life of the individual becomes more complex.

Problems which have a psychologic basis may be approached successfully in many cases during the early years by directing our therapeutic measures toward the environment and the child's personal relationship. In dealing with the preadolescent and adolescent behavior problems, the contact between physician and adolescent becomes more direct and intimate. The child assumes a more active part in the doctor-patient relationship. Without going into the details of the indirect and direct method, it is recognized that the latter is more complex and time-consuming and requires a greater facility and more experience with psychiatric disciplines.

By the end of the first decade, the average child has slowly but progressively become a fairly well-coordinated organism. There appears to be some mechanism which permits an adjustment between the child's appetites, desires, and feelings and the opportunities which society provides for a satisfactory, if not complete, fulfillment. This complacency of the preadolescent years is often rudely interrupted by disharmonies between anatomical growth, psysiologic changes, and psychologic drives—appetites and desires which heretofore have been slumbering peacefully. Since disharmony between growth, function, and emotion is often the basis of many of the adolescent behavior problems, the wisdom with which these problems are handled at their onset will often determine their permanent influence on the personality pattern. The psychologic implications of these situations should be common knowledge to every pediatrician.

If the pediatrician is to extend his services through the adolescent stage, it will become more and more important that his training in the field of mental hygiene be broadened so that he may deal wisely with these important psychologic problems of the adolescent period.

I am again stressing the need of more adequate training in our undergraduate and graduate courses and during the period of internship for those who are going into the field of pediatrics in order that they may utilize to full advantage the opportunities which their particular field has to offer mental hygiene.

DR. GARDNER.—Dr. Thom has stressed for you the responsibility of the pediatrician for the general and total care of the child in the earlier years of life and has emphasized the necessity for the pediatrician to recognize the importance of the emotional life of the child—and this particularly in the first decade. If I interpret my role on this program correctly, I am to emphasize and extend the notions of Dr. Thom, with which I may say I heartily agree, with particular reference to children in the adolescent years.

Of course we do not know what is meant by the term adolescence except that most of us, both pediatricians and child psychiatrists, assume that it in some way coincides with the age group of 12 to 16 to 17 years, or that it indicates those ages from the onset of puberty to a period of years—three or four perhaps—directly afterward. And just as adolescence is not a temporal or biologic entity, I would stress with greatest emphasis that it is not a distinct behavioral entity either. For all of these reasons and others that I will mention, I am more and more convinced that the gradual extension of pediatric care, with all that that should imply today in relation to personality development, to children beyond the age of puberty is a desirable thing. I do not know the origin of 12 years or the

onset of puberty as the upper age limit of pediatric responsibility, rather than the 17-year level which we tend to follow in child psychiatry, but I must hasten to add that the inclusion of the years to 17 as our field of operation was not due to omniscience on the part of the psychiatrists but was a happy choice on the part of the legal profession, who years ago said that the lawbreaker is a juvenile until he reaches the age of 17 years, after which he magically becomes adult. And inasmuch as child psychiatry was at first concerned with juvenile delinquents, we have followed this age group more or less rigidly ever since. However, I shall look for other determinants than criminal responsibility in emphasizing my opinion that a concern for the emotional and psychologic growth of children to this age limit is peculiarly the role of the pediatrician.

If there is one factor of child life that is of equal importance to those who practice the specialty of pediatrics and to those who specialize in child psychiatry, it is, it seems to me, the factor of maturity. To be sure, it may be of secondary value compared to the prime importance of prevention and cure of definite diseases, on the one hand, and the prevention or alleviation of definitely disabling neuroses on the other; but the ever-present peripheral problem of maturity (or lack of it) —physical and emotional maturity—must engage the attention of both groups of specialists and enter largely into their decisions in practically every case. And when one considers the problems called "adolescent problems," the pediatrician who has years of experience in the study and observation of growth and maturation of children in general and of a child or family of children in a particular family group should be in the best position possible to handle the behavior deviations that arise. It is the *longitudinal* study of the child and the data accumulated in his early years that is all-important in dealing with the adolescent, for behavior difficulties of the child of the teens are not symptoms of reactions to some newly imposed stress that can be understood only by cross-section study. On the contrary, they are the results of failure to mature emotionally, and the origins of this failure would seem to have their bases in the earlier deviations or arrests of the child's development, anomalies that the pediatrician cannot recognize at their inception. And when I speak of maturation, deviations or arrests in development, I make particular reference to the growth of the child in his reactions to people—the gradual emergence of his ability to handle adequately at each successive age level his interpersonal relationships in a manner expected of a child at that age.

What is most needed to meet the adolescent problem is the data accumulated in the first decade of life—data relative to the family set-up, emotional balance of the parents and siblings, position and rivalry, response to demands for sphincter control, eating habits, physical disease, school progress, response to pain, frustration—all of which are observed year by year by the pediatrician as they concern his particular patient. Furthermore, he has his general information regarding many children, which he may use as norms of behavior.

Two questions might come to your minds as you consider my opinion that pediatricians are in an excellent position to extend their care to the age of relative emotional maturity rather than to the age of physical maturity or puberty. The first question might be "Is there not something in the problems of the adolescent that sets him apart from those of the earlier years?" And the second question might be "What types of problems does the child psychiatrist consider to need the child psychiatrist's care, if most adolescents could be followed, and adequately treated, by the pediatrician?"

As regards the first question, it seems to me that there is very little that is distinctly peculiar about the trials and tribulations of the adolescent as compared to the problems in the early age group. They center, as does instinctual demands and needs and the opportunities that society allows for the direct or indirect fulfillment

of those needs. In early life society expects and condones certain modes of expression; society frowns if the child has forgone or modified the expressions of some of them twelve months later, some others six years later, and finally some must be remodified time and time again if the child is to be considered mature at each successive age level. It is the attempt to hold to or revert to the earlier modes of response as they may have been adopted by him as a child that usually brings the adolescent into difficulties. As examples, he will insist on the fulfillment of his needs at the moment, as he did successfully in babyhood, instead of the mature devise of postponing present desires for future greater benefits; he may respond to frustration with a rage reaction or aggression that should have passed with the elimination of the temper tantrums years before; or, reality becoming too harsh, he may find the compensatory daydream to be still as satisfying as the fantasy life of early childhood. Such is the core of the adolescent's problem, and it is best understood and handled in the light of information gained as to the failures or successes made in the years of infancy and childhood. The peculiarity that attracts our attention in the later years is usually the curious admixture of mature responses in one situation with definitely infantile responses in another. We forget that growth and maturity in an emotional sense follow as uneven a curve in the *individual* child from 12 to 17 years as the biometricians have pointed out to us obtains in the realm of physical growth in these years. Hence, though the problems involved may be *fundamentally* the same, and in this connection I do not accept the alleged emergence of the sex drive as an exception, the paralleled exhibitions of infantile and adult behavior as reactions in these children present us many times with a bizarre and baffling picture. This unpredictability of his behavior is a symptom of the unevenness of growth in this period.

As to the second question, the role of the child psychiatrist in treatment, I think I may speak for my colleagues when I say that the child psychiatrist of today is anxious to confine his professional attention to emotionally *sick* children—to those children whose atypical behavior is so complex, so patternized, and so deep-seated that without a successful use of the technique and skills that we have thus far evolved in our field, the child seems definitely headed for a life of social and economic inadequacy and perhaps mental ill health. The sooner the child psychiatrist's practice is confined to the treatment of these patients, the happier he will be.

In conclusion, I will add as pertinent to this meeting of members of allied fields in child care that the Mexican medical profession and some of our colleagues in other countries to the south of us recognize a peripheral specialty which they call "psychopediatrics."

DR. HARTWELL.—I would like to make a few remarks with the hope that we can start a discussion. I tell my students that they are not going to have an easy time in practice unless they know something of psychiatric relationships. I recall the parents of a diabetic child. They did not want the child and hoped she would die of her diabetes. Another child, a boy with contractures of the muscles causing deformity, was recommended for operation. When he got a release from a reform school he recovered from his contractures without operation.

I practiced general medicine for fifteen years before specializing in psychiatry. During that time I found out that what I said to my patients was what made them get well, not the medication they received. It behooves pediatricians to take an interest in mental hygiene. I tell students that they are going to have more fun, enjoy getting along, and be more successful if they understand their patients and have a knowledge of the child's problems.

Of course pediatricians should consider mental hygiene! They should be able to tell whether the child is frightened, confused, or whether anxiety is combating

these conflicts. The pediatrician should also know some theories. The child may be confused because parents are not able to cope with his problems. We are convinced that many difficulties occur between 6 months and 2 years of age in the children whose parents do not love them. The pediatrician sees him at this age but we psychiatrists do not see him until much later, and by that time the damage is done.

I wrote a book a few years ago called "Fifty-five Bad Boys," which covered a two-year period. I do not know what I did to help these boys but some of them came to see me after several years to thank me. We need pediatricians coming to orthopsychiatric meetings to tell us what it is all about.

In Buffalo we had three pediatricians coming to behavior clinics for one-half day each week and functioning as mental hygienists. Now they carry on in this capacity in their own practices. In Buffalo, people pay pediatricians good fees for mental guidance. They bring their children to the pediatrician for guidance just the same as for physical examination and urinalysis. When I hear pediatricians discussing enuresis from the standpoint of a genitourinary cause, I always ask them if they know of any kidney disease that causes enuresis. I hope we can have a discussion on some of these problems.

CHAIRMAN PLANT.—The six points of this presentation are condensations of an article appearing in *The American Journal of Diseases of Children.**

1. There are many values to the pediatrician's entering the field of conduct disorders, but he should not do so unless he is ready to face the fact that in at least five respects he must alter attitudes that have been accepted as basic in the discipline of medicine.

2. "Efficiency" (in behavior) is in terms of "the environment in which the child lives." In the physical field we want to develop the body or any organ to its highest potentiality in terms of itself. In the mental field and that of conduct, development is efficient in terms of its fitting the cultural and intellectual levels of the group with which the child lives and will live.

3. Conduct is determined by values—by what the child is looking for, what he thinks is worth while in life. In *this* field the physician is no more expert than is his patient. The traditional position of command, of leadership, which is essential in the physical field must be given up. When the child asks "Well, what *is* worth while?" the physician can only answer "I wish I knew, let us find out."

4. The field of behavior demands collaboration with other workers—and a sharing of responsibility with them. Teachers, recreation workers, social workers can all do jobs in this field that you cannot do—and know far more about certain aspects of human relationship than do you or I. If you can afford to use people only "to get something done that you want done," you had better stay out of the field.

5. You will meet an entirely new conception of frustration. Frustration in the physical field is usually benign—it is imposed on parts of the body when there is danger of fatigue or overuse (satiety in a number of fields as a good example). In the field of behavior, frustration is imposed from without.

6. You will meet a new concept of "vulnerability." In the physical field this is synonymous with "weakness"; in the field of conduct it is often synonymous with "strength." That is the child who comes to you as a conduct problem, that is the child who is most sensitive to the social pressure about him—and is often the child with enough intestinal fortitude to try to do something about those pressures. That is not to say that he is necessarily doing the *right* thing about them; but it is to point out that often the difficulty arises precisely from the strength and efficiency of the patient. It is not always easy to collect fees when one treats a certain conduct disorder with a hearty slap on the back and a cheery "Keep it up, old fellow, you're doing fine."

*Am. J. Dis. Child. 61: 347, 1941.

DR. GARDNER.—There is but one point that I would like to emphasize in speaking to this group of pediatricians this morning, and that point is that the so-called "problem child" should be looked upon as an individual whose socially unacceptable behavior is an ill-chosen and inadequate solution to an inner feeling of irritation, frustration, deprivation, or loss. His solution is a symptom, in the rather loose way in which we use the word symptom in medicine today, or a sign that can be interpreted only as indicating the total response of the organism to a real or imagined threat.

In the realm of behavior we may with profit, I feel, borrow much in both terminology and concept from the field of general medicine. It is a truism in pathology that the organism, when encountering a foreign body, an irritant, or pathogenic organism, sets in motion a host of *defensive* measures designed by nature to eliminate or render innocuous this intruder. For purposes of analogy I submit the proposition that in many, many instances it is the *defensive* measure *itself* that we call the disease, and this comes about only when the defensive measures demanded are so great and so overwhelming that they make impossible the normal functioning of the affected organ, and this in turn may so affect the total physiology as to cause death. I cite the reaction of pulmonary tissue to the pneumococcus or the cellular reaction to irritants known to produce neoplasms as examples of bodily *responses* originally designed as *defensive* measures that can and sometimes do become disabling. They are, we might say, biologically poor solutions of a problem.

It is helpful, I believe, for the medical man, and particularly the pediatrician, to view socially disabling *behavior* in somewhat the same light. Let us trace this problem of attack and defense as exhibited by the "problem child" through the outline of a few concepts and the example of a singular case.

As stated above, it seems to me that most of the behavior deviations in children are responses to the frustration of some fundamental need, some urge, some desire. The need in early life is usually traceable without great difficulty to a definite biologic craving, and though the same origins probably exist in the older child, the complexities and symbolism used may so cover the basic origin of the need that only specialized techniques and intensive investigation can uncover it. At any rate, be the need superficial or deep, the child in his behavior will, directly or indirectly, satisfy it if he can. If he is allowed to do so because his particular environment (his family, tribe, or community), grant avenues of expression to and gratification of such needs, his responses are called "good," his behavior is called "normal." He has no frustration, he feels no irritation, he needs to call into play no defensive measures.

But what are some of the defensive measures, some of the solutions, that he can resort to behaviorally when his needs are not satisfied—and particularly what are the solutions he may use that carried to the extreme render him obnoxious, inadequate, even menacing, and gain for him the label "problem child"? (1) Foremost in importance is the mechanism of repression. Through threat of pain or loss of parental affection to follow his direct unmodified satisfying of a need, the child learns that he must control his impulses through restrictions that *he himself* makes a part of his being. This is perhaps the most universal solution to this problem of instinctual drives versus society's demands, and though this solution seems to be a particularly harsh one and may break down later on occasion, it is hard to see how a complex society could regulate itself—or, in fact, even emerge—without its help. (2) Another solution may be the selection of an indirect expression of his need, or sublimation, if you wish, in behavior that is acceptable to society or in activities so disguised in their manifest nature that the original purpose is lost sight of, or at least so disguised that the fulfillment of basic needs is no longer considered the principal purpose of the behavior. Games and play (solitary and group), hobbies, interest, clubs, and avocations may be cited as solutions by sub-

limation. (3) Again the child may resort to fantasy and daydreams as the solution to his problem of frustration, deprivation, or loss. This defense or protection is universal in childhood where his comparative weakness and inadequacy are forever being brought to his attention merely perforce of his own observations. And as regards all of these solutions, repression, sublimation, or a host of other devices, the defensive measure of fantasy does not become a "problem" unless carried to an excess such that the child's efficiency, measured with the child's age standards, is impaired. (4) Another device we observe many times is the exaggerated overreaction against frustration and unbridled aggression toward the object or toward all of the objects (usually a parent or parents) causing the frustration as a solution used sometimes by the child.

To emphasize my single point that the "problem child" is a child attempting to solve a problem, I will give briefly a case illustration:

J., a 13-year-old boy in good physical health, was referred to the psychiatrist by way of the juvenile court and a social agency. He was brought to the court because he had repeatedly run away from home, had been discovered living in basements, getting his food wherever he could. He denied ever stealing, and no proof that he ever did was found. His runaways had carried him as far as six hundred miles from Boston. His father could do nothing with him; they quarreled incessantly, particularly over the boy's refusal to stay in the house nights. The father dated the onset of this incorrigibility to two years previous when J.'s mother died. Since then the boy's behavior had become steadily worse. The school officials stated that J. had received nothing less than B in his studies until two years ago, and usually led his class with straight A's. Since that time his work in school had slumped—he seemed inattentive and abstracted, and finally because of his repeated truancies, he was about to be placed in Disciplinary School. His only interest seemed to be in things chemical and he worked with a chemical set at home. The psychologist at the clinic found J. to have an I.Q. of 130—a very superior boy who should be able to do high school and, later, college work creditably.

Here, certainly, is a "problem boy." But if we trace back with him step by step each bit of behavior which you deem abnormal, atypical, or bizarre, you will see, I think, that each and every bit of it refers to his attempts to solve for himself the overwhelming problem of the death of his mother. Because of circumstances in the home, he perhaps had an even stronger attachment to his mother than most boys at his age do, and the frustrations attendant to her loss called into play a galaxy of solutions—but none of them were satisfactory because he did not really consider her dead—and some of which led him to the juvenile court. I will cite examples. In the first place, his greatest hatred was for doctors, and he told me so in his opening sentence in my office. (Not a very favorable setting for the application of psychotherapy.) He stated that he hated doctors because they killed his mother. Asked how he came to believe that, he said that his mother died of pneumonia on the eighth day of her illness, and he knew that pneumonia patients do not die till the ninth day; hence the doctors killed her on the eighth. (You can see by his method of reasoning the doctor was not guilty of a mere omission of adequate therapeutic aid—because she should have lived till the ninth day anyway. Hence they did something that prevented the patient dying, as it were "normally" from pneumonia.) J. had many ways in which he was going to solve the problem of doctors, but up to the present time he had contented himself with letting the air out of their tires, ripping off the number plates, green crosses, and an occasional caduceus that he saw on cars parked on what can best be described as Boston's "Harley Street."

J. hated his father because he did not call the doctors in the early days of his mother's illness and hence had contributed to her death. His father had not been kind to her. He would never again obey him and he would accept nothing from him.

As to his loss of interest in school and his failure to do school work he explained that he had lost all interest in school because it was his mother for whom he worked at his lessons, and without her there to approve his efforts and shower him with love and approbation for his good efforts, he could not study. Furthermore, in the stillness of the schoolroom he daydreamed about her, and these fantasies were so vivid and so satisfying that he would actually convince himself that she were alive, only to be rudely brought to earth by the teacher's admonitions that he stop dreaming and pay attention.

Finally, and more fantastic than all, were the ramifications of this problem into J.'s seemingly normal boy's interest in chemistry and its association with the solution that brought him to the court, his running away. Contrary to what you might expect, he did not run away primarily to be away from his father, but ran away to visit museums in various large cities. He visited museums to observe and study Egyptian mummies and to learn as much as he could about the preservation of the form of the human body after death. (I hate to stress the association between mummy and mother, but "mummy" was actually what he called his mother when she was alive.) His information in the field of Egyptology was enormous for a boy of his age, even making allowances for his very high intelligence quotient. From this originated his interest in chemistry, and he studied chemistry with a twofold purpose, first, to prepare, if possible, a fluid that could be injected into the veins of the dead in order that they might be preserved life-like forever and, secondly, to discover a chemical that would eradicate pneumonia. By the latter discovery he was as much interested in the fact that it would enable *him* to tell doctors how to treat patients as he was in the contribution which he thereby would make to the welfare of humanity as a whole.

I will give you none of the details of the therapy in this case and will close it by saying that after treatment and a period of foster home care the boy returned to his own home, is still there, and seems to be doing well.

However, I hope that this *single* example with the varied behavior that this boy used in an attempt to solve his problem will serve to illustrate the point drawn that the "problem child" is really a child who is trying to solve a problem.

DISCUSSION

DR. S. F. RAVENEL, GREENSBORO, N. C.—Could Dr. Casparis and Dr. Aldrich reconcile their statements regarding courage?

CHAIRMAN CASPARIS.—There is no discrepancy. We must be realistic and reasonable. Dr. Aldrich's remarks were regarding the infant before cerebral development. It is reasonable to adjust ourselves to the infant's rhythm.

DR. ALDRICH.—We do not advocate giving the children what they want but to satisfy their needs. The child who has an outgoing personality and is cheerful will be amenable to advice.

CHAIRMAN CASPARIS.—We must live up to our level of accomplishment at any level.

DR. J. E. RUSSELL, JR., DENVER.—What is the relative importance of heredity and environment?

CHAIRMAN CASPARIS.—We do not have to know. We must build as good a structure as we can. We never know the quality of heredity but find out as we go along.

DR. RUSSELL.—I mean more the child who is born of high-strung, jittery parents.

CHAIRMAN CASPARIS.—They are hard to deal with. Such children offer more trouble but are well worth it. We often hear of the "black sheep." Usually he is the smartest one but was not handled in a manner commensurate with his needs.

DR. LANG, NEW YORK.—What concrete suggestion can you offer on how to develop breast feeding on a newborn service.

DR. ALDRICH.—This goes back to a fundamental question of the organization of newborn services. I would like to see babies in the rooms with the mothers. One mother had six children and said, "Your nurses don't know their stuff. They put the baby in bed and push the baby's cheek with their hand," whereupon the baby instinctively turns toward the hand.

DR. T. P. SALTIEL, CHICAGO.—Behavior in the nursery is far better when it is air-conditioned.

CHAIRMAN CASPARIS.—Would Dr. Beverly please comment on this subject?

DR. B. I. BEVERLY, CHICAGO.—I was in hopes Dr. Aldrich would go farther about trying to get mothers, obstetricians, etc. to realize that the mother needs the baby as well as vice versa.

DR. ALDRICH.—By hard work.

DR. E. P. RUSSELL, BERWYN, ILL.—In regard to children clinging to familiar things and fearing strange things, what effect does frequent moving have?

CHAIRMAN CASPARIS.—We are always running into situations where adjustments must be made. It places more responsibility on the parents. It takes time to assist children in making adjustments.

DR. ALDRICH.—After all, is not that a minor adjustment? If they are secure in their mother and father, the adjustment is easy.

MRS. DAVIS, BOSTON.—Do you not think the pediatrist might help more in these adjustments by advice in regard to time? Would you like to comment, Dr. Beverly?

DR. BEVERLY.—I would only like to emphasize what Dr. Aldrich said about security in parent's affection.

CHAIRMAN CASPARIS.—Just because we complain does not necessarily mean that we are fundamentally disturbed.

DR. ALDRICH.—Mrs. Davis had a point which we may have overlooked. Namely, do not pile troubles on one another.

DR. RUSSELL.—Does religious instruction undermine confidence in parents?

CHAIRMAN CASPARIS.—The child can only benefit by learning at an early age that father is not a god and mother not an angel. It can be explained that the Sunday school teacher is talking about extremes.

DR. ALDRICH.—There is a developmental angle that no child under 10 years of age is capable of abstract thinking. This is more important in adolescence.

DR. S. D. POSSON, ROCHESTER, N. Y.—What attitude should we take when the parents want us to give a confidential talk on masturbation?

DR. ALDRICH.—Masturbation is part of growing up. Talk to the mother first and then possibly to the child.

DR. MARGARET E. FRIES, NEW YORK CITY.—In regard to abstract thinking, is it not more important what parents do? They are, for example, living in a democracy but may be treated undemocratically.

DR. F. W. ROGERS, MANCHESTER, N. H.—Do you find that the smaller the family, the harder the problem?

DR. ALDRICH.—The larger family has more opportunities to teach the child to give and take.

DR. J. E. RUSSELL, JR.—How should one handle solid food habits? Should they be forced?

DR. ALDRICH.—These need not be problems. Anyone but an idiot will grow up and take solid food when ready. I never saw prolonged forcing do any good.

CHAIRMAN CASPARIS.—This goes back to liking pleasant things and disliking unpleasant things. In starting new experiences, we must be very careful not to make things unpleasant.

DR. RUSSELL, JR.—But we are taught that they must have certain foods.

DR. ALDRICH.—Again we must recognize the developmental trend. Most babies will try anything up to a year. After that (2 to 4 years) they specialize in "old friends." This widens automatically.

DR. GEORGE K. HAGAMAN,* ST. PAUL.—What about the child who refuses to have a bowel movement on the toilet but will have it as soon as removed (in the corner)?

DR. ALDRICH.—I would want to know what happened at 6 months. Something has made him angry about the whole thing, and you will not get anywhere until he gets over being mad. Often if allowed to go themselves, they will be all right.

DR. BEVERLY.—It is nearly always the second youngster and some resentment.

CHAIRMAN CASPARIS.—I am particularly interested in promoting cooperation with the schools. I suggest that we simplify our instructions to the teachers.

DR. F. H. DOUGLASS, SEATTLE.—Is it possible to work out a textbook of facts for the use of teachers? Health facts for different grades?

DR. MITCHELL.—A great deal has been done to meet this need. The present thought is that hygiene can best be taught otherwise than out of textbooks.

DR. L. A. WILKES, TRENTON, N. J.—Dr. Mitchell, can anything be done to promote cooperation with the pediatrician and the school physician? Perhaps by the Academy?

DR. MITCHELL.—That is the very point I am trying to emphasize. It has been done in many places and can be done when local pediatricians take an interest.

DR. ALDRICH.—We should emphasize the importance of prevention. This problem has been thrown in our laps. It would be impossible to cure all the behavior problems, but we must take on the project of preventing. Therefore, less emphasis on child guidance clinics and more on what anyone is doing in his office.

CHAIRMAN CASPARIS.—These children are going to run things in the next generation. We will be responsible. After all, it was the attitude of the popula-

*Deceased.

tion which ruined Roman civilization and we have to face the job of forming the attitudes. Children want friendship and companionship with parents and not presents offered in conciliation for having neglected them.

DR. ROGERS.—What about the development of love in children? Is it proper to tell parents to develop respect first?

CHAIRMAN CASPARIS.—Do not separate them.

DR. ALDRICH.—They want a place in the home; to feel that they have to belong.

DR. J. D. CRAIG, NEW YORK CITY.—What about the child who vomits on school days only.

DR. ALDRICH.—This cannot be answered on a superficial basis.

CHAIRMAN CASPARIS.—If it does not get him anywhere he will discontinue it.

DR. ALDRICH.—We have not stopped that problem when he stops vomiting.

DR. M. R. WOODWARD, SHERMAN, TEXAS.—You have stated that the age limit of pediatrics should be extended through adolescence. Where and how will the average pediatrician obtain the necessary information to prepare him in this field since it presents special problems?

CHAIRMAN THOM.—All pediatricians can get a great deal of information by keeping in touch with the current literature relating to mental hygiene and also from actual practice. One profits from experience and realizes that concepts of mental hygiene deal very largely with treating the patient rather than the disease. For those individuals who are living in or near a medical center, facilities are available for postgraduate work.

DR. WILKES.—What is the degree of correlation between physical and emotional development during adolescent years?

DR. GARDNER.—I think we know very little about the correlation between these factors in adolescence. We know there are definite, even drastic, physical changes going on and we also find many adolescents who are disturbed emotionally, but they do not necessarily coincide as regards time. For instance, they do not always occur at that period of maximum growth near puberty which is one measure of changes taking place.

However, these changes themselves, or the *lack* of them sometimes create worries for the child, and this is particularly true of many adolescent girls. A delay in development causes concern as to whether they are developing "normally" as are others of their chronologic age. Many of them need reassurance on the questions, "Am I as mature as I should be at that time?" or "Will I in one year measure up to what I should be at that time?"

By way of digression I would like to emphasize Dr. Hartwell's point that in many of these problems the physician must instruct the child, as the parents' inhibitions prevent them from doing so. Above all, the child should be prepared, through sympathetic discussion, when any surgery is to be resorted to.

DR. C. F. WEINFIELD, HIGHLAND PARK, ILL.—Children fear circumcision. They also fear tonsillectomy. Do not operations of this sort cause trouble?

CHAIRMAN THOM.—Yes, I think that is so.

DR. D. P. EVANS, EAST ORANGE, N. J.—Do you think it is advisable to have parents undress in the presence of the child before two years of age so that children see both parents naked? Is there any harm in this?

DR. HARTWELL.—I think it is the best technique possible.

DR. GARDNER.—At an early age, yes, but at 4 or 5 years it may not be so desirable. In order to eliminate fears, the parents should tell the child that he will be the same later on as they are now.

DR. HARTWELL.—Certain parents with fears and anxiety create fears in minds of children simply in the way they carry out sex instruction. Penis envy or castration complex is of great importance and must be taken care of. The child should learn early that sex is not something to fear.

QUESTION.—What is your attitude in regard to mother holding offspring and rocking them to sleep? I refer to the baby during early infancy. What is the earliest application of mental hygiene in infancy?

DR. GARDNER.—There is no objection that I can see to a mother rocking her infant. A child can be taught, however, that he can go to sleep by himself. Every child should be a wanted child and this brings up the matter of security. In habits of eating, bowel control, etc., the child can be given the feeling of security. He can detect whether there is a break in proper parental relationship.

DR. E. S. FISH, BEVERLY HILLS, CALIF.—Should not the child be taught early that temper tantrums, for example, are antisocial and should not the cause of the tantrums be avoided? Are not families too soft?

DR. HARTWELL.—We should find the cause of the temper tantrum and then find a way to let him work through it. Let him know that temper tantrums do not work.

DR. JACK BASMAN, CHARLESTON, W. VA.—What importance do you place on the so-called lack of cerebral dominance?

DR. HARTWELL.—This is controversial. If there is a change in handedness, they are liable to be emotionally tense.

CHAIRMAN THOM.—Problems related to cerebral domination are usually due to the fact that left-handedness, for example, may create in the individual a feeling of being different or perhaps some awkwardness attracting undesirable attention which represents the problem and not the cerebral situation in itself.

DR. WILKES.—What factors act in changing behavior in late adolescence?

CHAIRMAN THOM.—Much of the undesirable behavior we see in the adolescent represents an effort on the part of the child to develop independently. Conflicts arise because he wants the privileges and the opportunities that go hand in hand with growing up, but he frequently resents assuming the responsibilities that are associated with independence. This is an important point that it is important for the child to understand.

DR. PARK J. WHITE, ST. LOUIS.—All of these problems, whether of sex education or of behavior, come to us gradually, in a manner analogous to physical growth. The pediatrician enters the picture—and sees it—for brief spaces only. But he sees all sorts of family situations repeatedly and intimately. If he does so wisely,

he is in an excellent position to advise patients, parents, and also grandparents. Incidentally, I always recommend the bathroom, rather than the living room, for intimatae family councils. Here, of course, is the place for gradual, natural, easy sex education, far preferable to the plan of having Dad or the doctor "take an hour" for an uncomfortable and long-deferred talk with a sophisticated adolescent.

DR. J. F. CLANCY, HAMMOND, IND.—At how early an age is it possible to suspect the potential dementia praecox individual?

CHAIRMAN THOM.—One may expect an individual to be a potential dementia praecox at any age. I do not think that a diagnosis can be made with any degree of certainty until the child has reached 8 years of age.

DR. JOHANNA HEUMANN, CHICAGO.—Granted that it is the pediatrician's job to talk to the child, whose job is it to talk to the mother or grandmother?

CHAIRMAN THOM.—This is the pediatrician's job. It is his responsibility to establish proper parent-child relationship.

DR. G. W. ESTY, WESTFIELD, N. J.—When I make my first visit to see a newborn baby, after I have instructed the mother in the general care and feeding of the infant, I try to build up a healthy attitude toward the newborn regarding mental health. I try to establish an attitude that will aid the baby in growing up. As a result of such preparation, they do better in school. In making a first house call on an older child I routinely get a history of behavior and emotional development.

DR. HARVEY SPENCER, WELLESLEY, MASS.—How can we modify the too prevalent feeling of many parents and teachers that passive submissive behavior is the most desirable model of behavior in children?

CHAIRMAN PLANT.—Pediatrists must consider this a cultural question, keeping in mind that a child is often trying to solve a problem by aggressive behavior. Also that this treatment may well be a joint effort; that is, through the effort of parents, P.T.A. groups, and the physician. As an illustration, an individual in his capacity as a father and also a doctor may tend to create confusion in the treatment of his own child. We are drifting toward a "total society," and in modern concentrated modes of living, there must be some submissive pattern, otherwise there will be chaos.

DR. SPENCER.—What institutional facilities are available (or should be available) for the predelinquent child?

DR. HARTWELL.—There are available in most states (1) child guidance clinics; (2) institutions for the treatments for the delinquents; (3) special classes in schools for the physically and mentally handicapped; (4) boarding schools; (5) correctional schools.

CHAIRMAN PLANT.—It is quite desirable that the pediatrist should sit in the classroom and observe the conditions and the behavior of the child there. "The problem child," if he goes to an institution, goes there as a symbol of complete failure.

DR. I. J. WOLF, PATERSON, N. J.—In the treatment of enuresis, do you believe the child should be awakened when taken to the bathroom?

CHAIRMAN PLANT.—Yes.

DR. GEORGE HELLER, ENGLEWOOD, N. J.—What should be done with the irritable child who cries a great deal at night?

CHAIRMAN PLANT.—Often this type of patient is the spoiled child, and the parents or relatives may often be responsible for this type of behavior. The treatment lies in the elimination of this type of parental influence.

DR. PHILIP C. ELLIOTT, NASHVILLE, TENN.—What do you think of private schools for boys and girls?

CHAIRMAN PLANT.—The child is ready to go to a nursery school whenever the feeling of belongingness in the home is established, whatever the age.

DR. HARTWELL.—In regard to the adolescent child that is in the age group of 12 to 15 years of age, this child does well for a year or two in a private school, whether a boy or girl.

DR. GARDNER.—Coeducation is recommended.

DR. W. R. PHILIPS, ELMIRA, N. Y.—What advice can you give in a case where the child had "night terrors" for two weeks?

CHAIRMAN PLANT.—The child should be reassured that the frightening experience has no reality, if the child is old enough. For a few nights, the crib should be moved to the mother's room in an effort to establish reassurance. Later the child should be moved back to his own room for some neutral reason; that is, the furniture has to be moved in the mother's room and the baby's crib will have to be moved back to his room. This will help, only if the condition is of a short duration, but if the situation is months' old, then the treatment is different, and it often requires a complete break in the care of the child, that is, a nurse or a relative must undertake such care for a time.

DR. GARDNER.—If possible, the reason for the fright should be definitely determined.

DR. HARTWELL.—Reassurance that may try the ingenuity of the parent must be tried.

CHAIRMAN PLANT.—Early in such affairs, mothers often feel they are failures; that is, they are morally wrong if the night terrors continue. The mother should reassure her child, and in doing this, feel she is doing right in spite of apparent failure.

The Pediatrician and the War

An Appeal

Several thousand children of Polish, German, Russian, Czecho-slovakian, Dutch, and stateless nationalities who are now in Southern France are in grave danger of deportation to Eastern Europe unless they are brought to America quickly. For the most part their parents have already gone or are likely to be deported immediately, and the children themselves are in a condition of forlorn hope.

The United States Committee for the Care of European Children, Inc., has undertaken to bring as many children as are eligible under the existing limitations and within the regulations of immigration procedure to the United States, where they will be placed in private homes. Many agencies are assisting in bringing the children from Unoccupied France, across Spain to Lisbon, and from Lisbon to the United States on neutral boats, which boats will sail with navicerts provided by the respective Governments.

Plans have been completed for a first escort party of seven doctors, six nurses, four nurses' aides, and twenty child care people who are used to handling children in large groups to go from this country to Lisbon, whence they will return with the convoy of children. The American escorts will be supplemented by additional escorts, carefully picked from refugees abroad. The returning steamer will be crowded, and there is considerable danger from epidemics, but even so, the temporary conditions of such a passage, bad as they may be, are far better than the only remaining alternative which faces the children—that of deportation into Eastern Europe. Thus, without question, as many children as it is physically possible to bring to a free country should be given such an opportunity.

A brief announcement at one Pediatrics Section Meeting of the New York Academy of Medicine recently produced enough volunteers among the doctors to more than cover the first trip. If this trip is successful, it is expected that there will be other trips in the course of the winter and spring, and doctors, nurses, and qualified escorts will be needed for these anticipated voyages. All volunteers must be citizens of the United States, have a special knowledge of either French or German, be willing to work almost ceaselessly on the eleven or twelve days of the return trip, be willing to do anything that needs to be done. Of the doctors, we need for each trip one surgeon, one child psychiatrist, and pediatricians. All expenses of each volunteer will be paid. Doctors will receive no additional honorarium.

Doctors interested in making such trips should communicate directly with:

Dr. Philip M. Stimson
25 Claremont Avenue
New York, N. Y.
(Monument 2-2112)

All others should communicate with:

Mr. Robert Lang, Director
U. S. Committee for the Care of European Children
215 Fourth Avenue
New York, N. Y.
(Algonquin 4-5162)

News and Notes

Children's Tumor Registry

The Executive Committee of the American Academy of Pediatrics has approved the establishment of a Children's Tumor Registry under the auspices of the Academy. The Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York City has been designated to develop the Registry.

Purpose.—Neoplasms, aside from hemangiomas, are unusual during childhood. The varieties of malignant tumors which occur in children may be more numerous than those observed in the adult. The mortality rate from cancer during childhood is extremely high. It is apparent that no individual or single institution can accumulate sufficient case material from personal experience to permit of sound general conclusions. The purpose of the Children's Tumor Registry is to gather clinical case records in a uniform manner with the hope that in time enough data can be acquired to warrant accurate conclusions for each of the many anatomic and histologic forms of childhood neoplasms from the following standpoints: (1) etiology and incidence; (2) pathology of childhood cancer and certain benign tumors; (3) difficulties in diagnosis; (4) frequency and reasons for delay in diagnosis; (5) average clinical course; (6) response to various forms of therapy (radiation, surgery, etc.).

Consulting Board of Pathologists.—The following pathologists will review the microscopic sections submitted to the Registry:

Dr. Sidney Farber, Boston, Mass.
Dr. Alvin Foord, Pasadena, Calif.
Dr. Howard Karsner, Cleveland, Ohio
Dr. Roy R. Kracke, Atlanta, Ga.
Dr. Robert A. Moore, St. Louis, Mo.
Dr. John R. Schenken, New Orleans, La.
Dr. Paul E. Steiner, Chicago, Ill.
Dr. Fred Stewart, New York, N. Y.

Varieties of Case Material.—

1. All malignant tumors including Hodgkin's Disease.
2. Certain benign tumors: (a) those that histologically are unusual; (b) those so situated in the body as to endanger life or to be incompatible with it.

Sources of Case Material.—All hospitals, clinics, and members of the medical profession are invited to submit preliminary data and microscopic sections on cases believed to be those of malignant tumors or of the varieties of benign tumors mentioned in the preceding paragraph. These data and slides should be addressed as follows:

Children's Tumor Registry,*
Memorial Hospital,
444 East 68th St.,
New York, N. Y.

If the preliminary review of these data indicates that the case is a proper one for acceptance, then forms will be returned so as to obtain further details including radiographs, etc. The Registry assumes the responsibility to collect and record follow-up information relating to the further clinical course and end-results in all cases.

Clinical Recommendations.—If so requested, the Registry will obtain and forward immediately opinions by recognized authorities as to the diagnosis and recommendations for treatment.

Custody of Records.—The case records of the Registry shall, for the present, be kept at the Memorial Hospital for Cancer and Allied Diseases and until the Executive Committee of the Academy of Pediatrics directs otherwise.

*The address of the Registry will be found in THE JOURNAL OF PEDIATRICS each month.

Abstracts of Food and Nutrition Research

Biological Abstracts announces the establishment of a new (seventh) section, "Specially Assembled Abstracts of Food and Nutrition Research" to be initiated in January, 1943. This section will consist of an assembly and reprinting of all the abstracts contained in *Biological Abstracts* that deal with human and animal nutrition and metabolism, vitamins, diet and diet-deficiency diseases, food composition and values, food processing and food microbiology, beverages, storage and conservation of foods, food spoilage and, in short, all of the biological literature that pertains to foods and nutrition.

In line with the general policies of *Biological Abstracts*, every possible effort is being made to insure completeness in coverage of the world's literature. Efforts to obtain abstracts of publications from continental Europe, now mostly unavailable to workers in this country, are continuing.

Each volume will consist of ten abstract issues; subscribers will receive the index to the complete edition of *Biological Abstracts*. The subscription price will be six dollars per year (plus fifty cents for postage outside the United States). Inquiries should be addressed to *Biological Abstracts*, University of Pennsylvania, Philadelphia, Pennsylvania, U. S. A.